Transient loss of consciousness in adults
Guideline Consultation Comments Table
20 January – 17 March 2010

SH = Registered Stakeholders. These comments and responses will be posted on the NICE website when the guideline is published.
PR = Peer Reviewers or Experts. These comments and responses will be posted on the NICE website when the guideline is published.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
PR	NETSCC, Health Technology Assessment Referee 1	1	Full	General	General	Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached) Very comprehensive coverage of the topics specified in the scope.	Noted with thanks
PR	NETSCC, Health Technology Assessment Referee 2	1	Full	General	General	Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached) No there are no ways in which this doesn't happen	Noted with thanks
PR	NETSCC, Health Techn	2	Full	48	15	2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual).	Figures were incorrect on cross checking – should have been 849 deaths (0.12%) above 19 years of age. This has been corrected.

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	ology Assessment Referee 1					Can the authors give an explanation of why the G40 epilepsy deaths are so out of line for 2004? Without a clear explanation of this 'outlier' one has to question the validity of all of data presented in the table at line number 8.	
PR	NETSCC, Health Technology Assessment Referee 2	2	Full	62	General	2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual). KCQ excellent	Noted with thanks
PR	NETSCC, Health Technology Assessment Referee 1	3	Full	58	13	The implication here is that there was a single individual who appraised the literature and abstracted the evidence, which would be poor practice. Can this be clarified? The comments on page 65 below relate.	Technical teams working on NICE guidelines normally contains one systematic reviewer (see NICE Guidelines Manual). In this (complex) TLoC guideline two reviewers worked on the guideline throughout and there was much cross checking of the evidence abstracted.
PR	NETSCC, Health Techn	3	Full	64	9	Diagnostic test study inclusion robust, exclusion on basis nos and age appropriate	Noted with thanks

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
	ology Assessment Referee 2						
PR	NETSCC, Health Technology Assessment Referee 1	4	Full	65	11	The eligibility was checked by a second reviewer 'where necessary'. What does this mean? It would be good practice for almost all of such work to be checked independently.	We agree that the ideal is for independent checking of all inclusion of papers. However, this is not usually possible within the time constraints of NICE clinical guidelines. 'Where necessary' means 'if there was doubt'. We have altered the guideline to reflect this.
PR	NETSCC, Health Technology Assessment Referee 2	4	Full	65	5	Sifting process clear	'Thank you. This is now corrected'.
PR	NETSCC, Health Techn	5	Full	66-67		I find no flaw or criticism with the critical appraisal procedure that is outlined	Noted with thanks

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
	ology Assessment Referee 2						
PR	NETSCC, Health Technology Assessment Referee 1	5	Full	65	17	Data extraction was 'usually' checked. What does this mean? Again it would be good practice for all the data extraction to be done independently by two individuals.	We agree the ideal is for data extraction to be done independently by 2 reviewers. This is not usually possible in the NICE clinical guideline timelines. For this TLoC guideline, however, much independent checking was carried out. We have edited the guideline to reflect this.
PR	NETSCC, Health Technology Assessment Referee 2	6	Full	68-70		Data synthesis beyond reproach	Noted with thanks
PR	NETSCC, Health Techn	6	Full	67	1	Is the word 'delirium' a cut and paste error? I don't see how it fits here.	Thank you. This is now corrected.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
	ology Assessment Referee 1						
PR	NETSCC, Health Technology Assessment Referee 1	7	Full				
PR	NETSCC, Health Technology Assessment Referee 2	7	Full	71-73	3	Well framed basis and excellently conveyed	Noted with thanks
PR	NETSCC, Health Techn	8	Full	72	12	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** A 50% relative risk reduction corresponds to a RR of 2, not 1.5.	The 'relative risk reduction' refers to the change in relative risk that constitutes a clinically important difference between interventions relative to the null effect. So a 50% increase on a RR of 1 is 1.5.

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	ology Assessment Referee 1						
PR	NETSCC, Health Technology Assessment Referee 2	8	Full	180	10	Well decided regarding study bias which is always a massive problem in retrospective ecg studies	Noted with thanks
PR	NETSCC, Health Technology Assessment Referee 1	9	Full	128	16	'One low quality study' – reference?	We have rearranged this chapter so that the description of index test, reference standards etc are immediately followed by the results (largely tabulated) for each sub-review (e.g. signs and symptoms for epileptic seizures). It should be clear now to which study is referred.
PR	NETSCC, Health Techn	9	Full	202	17	I understand why making a research recommendation but I really dont think its ever to be achieved isnt it more correct to state there is no evidence of an acceptable quality	We have not found any published studies comparing diagnostic test accuracy of automatic versus manual ECGs that specifically state that all the patients had TLoC. However, we accept that some of the patients in the

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	ology Assessment Referee 2						reported studies may have had TLoC and we note the unpublished study we have reported. Therefore we have modified the research recommendation, to say, "no published scientific studies are available in a population selected for TLoC"
PR	NETSCC, Health Technology Assessment Referee 1	10	Full	129	Table	I think there is a fundamental problem with this table, and with later similar tables. It classifies the strength of a predictor in terms of its LR with little consideration of the precision of the estimated LR. With a very small sample size the point estimate of the LR could be 11 without the LR even being statistically significantly different from 1. A proper classification of the strength of a predictor would need to take account of the magnitude and precision of the point estimate, and also assess the likely biases.	Thank you for your comment. In the consulation document we did not include studies that had a LR that crossed 1. However, we accept that we had not explicitly taken into account the precision of the estimates. The tables now include the point estimates with their 95% confidence intervals. Although GRADE processes are currently not available for diagnosis questions, we carried out a GRADE-like analysis for the diagnostic test accuracy results, taking into consideration directness of the population, inconsistency and imprecision, reporting an overall evidence quality for the predictors. We have also included 4 new studies across these reviews. We believe this re-work has strengthened the reviews and, in some cases has led to changes to recommendations.
PR	NETSCC,	10	Full	344	15	There are lots of assumptions built into this when you reread but I would think they appear to be reasonable	Thank you for your comment

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	Health Technology Assessment Referee 2						
PR	NETSCC, Health Technology Assessment Referee 2	11	Full	72	9	2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise. As a non health economist I find the diagnostic test analysis easily understood and justified. I think that the ensuing several pages will be poorly understood by the practicing clinician brief consultation with colleagues in medicine revealed similar	Thank you for your comment. We appreciate that the technical details of the economic analysis may not be accessible to all clinicians who will be implementing the recommendations.
PR	NETSCC, Health Technology Assessment Referee 1	11	Full	130	4	It would be useful to tabulate the adjusted ORs (with 95% confidence intervals) to quantify the effect of the different predictors in the multivariate model.	The tables now include the point estimates with their 95% confidence intervals.
PR	NETSCC,	12	Full	146	12	It would be useful to tabulate the adjusted ORs (with 95% confidence intervals) to quantify the effect of the different	The tables now include the point estimates with their 95% confidence intervals.

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	Health Technology Assessment Referee 1					predictors in the multivariate model.	
PR	NETSCC, Health Technology Assessment Referee 2	12	Full	330	General	This section actually is well written and very amenable to non economists!	Noted with thanks
PR	NETSCC, Health Technology Assessment Referee 2	13	Full	83-87	General	3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected? The clinical questions are those that require answering and are well chosen and relevant	Noted with thanks
PR	NETSCC,	13	Full	181	15	Here, and in many other similar tables, there is no indication of the precision of the estimated sensitivity,	The tables now include the point estimates with their 95% confidence intervals.

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	Health Technology Assessment Referee 1					specificity, etc.	
PR	NETSCC, Health Technology Assessment Referee 2	14	Full	63	General	Are any important limitations of the evidence clearly described and discussed? Search details and conduct exemplary obviously - I agree with abandoning heand searching in particular in area such as this	Noted with thanks
PR	NETSCC, Health Technology Assessment Referee 1	14	Full	191	4	Here, and for many other similar figures, I think it would be clearer to describe the curve as a 'Summary ROC curve' rather than just a ROC curve. In this instance the figure strikes me as overkill when all the relevant data are tabulated very clearly in Figure 4.2 above.	We have removed the ROC curve plot
PR	NETSCC,	15	Full	27	Gene	4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for	Thank you for your kind words.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
	Health Technology Assessment Referee 2				ral	example, it is easy to understand how the recommendations have been reached from the evidence. Extremely readable very easy to use flow chart that covers text very well	
PR	NETSCC, Health Technology Assessment Referee 1	15	Full	192	4	Why are 2 studies shown in the Figure when the corresponding text only mentions one study?	This has been corrected
PR	NETSCC, Health Technology Assessment Referee 2	16	Full	55	16-17	Excellent section very well stated	Noted with thanks
PR	NETSCC,	16	Full	194	3	Throughout this section it must be made very clear that even if the authors are just summarizing the results from	Thankyou for your comment. We have removed the correlation statements.

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	Health Technology Assessment Referee 1					the source references, correlation is meaningless as a measure of agreement between two methods of measurement. Suppose that an automatic determination of HR was always 34 bpm less than five times the manual determination. The correlation would be 1 but the agreement rubbish!	
PR	NETSCC, Health Technology Assessment Referee 2	17	Full	93	General	Comprehensive glossary that excludes no terms that I could see	Noted with thanks
PR	NETSCC, Health Technology Assessment Referee 1	17	Full	234	4	The scale of the graph needs to be modified as a proportion cannot be negative.	Thank you for your comment. We accept that for some of the studies, the simple formula we used to calculate standard errors was inappropriate (e.g. small sample size). We have now calculated asymmetric confidence intervals for all these data and replotted the graphs on appropriate axes.
PR	NETSCC,	18	Full	100-	Gener	Whilst this is clearly relevant and is exhaustively inclusive it is difficult to assimilate as it is so similar However it is very	Noted with thanks

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	Health Technology Assessment Referee 2				al	well synthesized into pages 170 on Evidence to recommendations	
PR	NETSCC, Health Technology Assessment Referee 1	18	Full	235	1	The software being used to produce the forest plots needs to be rethought as here as in many, many subsequent figures it is producing confidence intervals for proportions which go negative! For example in this figure the problem is with Brignole 2001, the first study under 5.72.4 IRL. Clearly the software does not handle small sample sizes appropriately.	Thank you for your comment. We accept that for some of the studies, the simple formula we used to calculate standard errors was inappropriate (e.g. small sample size). We have now calculated asymmetric confidence intervals for all these data and replotted the graphs on appropriate axes.
PR	NETSCC, Health Technology Assessment Referee 2	19	Full	39	10	4.2 Please comment on whether the research recommendations, if included, are clear and justified. Increase in admissions as short stay? coincident European guidelines issued at roughly the same period. I think it needs to be emphasised? that this is in line with safe practice rather than a waste of bed days - unclear whether a non clinical reader would interpret this in that way	Accepted. However, The European guidelines mention under Point 1.6 that roughly 40% of patients presenting to ED are hospitalised. The figures for the UK appear to be higher (~75%). The same point also refers to the inefficient use of resources in the management of patients with syncope. Point 5.3 in the ESC guidelines stress the need for adequate risk stratification for these patients in order to improve diagnosis and decrease hospitalisation.It is unclear from the data for the UK whether any risk stratification was undertaken and whether all those admitted fell into the high risk group and hence constituted

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							safe practice.
PR	NETSCC, Health Technology Assessment Referee 1	19	Full	237	5	A very similar problem. Confidence intervals for observed proportions of zero are being reported as not estimable when there are perfectly adequate statistical procedures for deriving such confidence intervals. The problem is with the software which has been chosen for these analyses.	Thank you for your comment. We accept that for some of the studies, the simple formula we used to calculate standard errors was inappropriate (e.g. small sample size). We have now calculated asymmetric confidence intervals for all these data and replotted the graphs on appropriate axes.
PR	NETSCC, Health Technology Assessment Referee 2	20	Full	53	General	NHS direct dta fairly frustrating to digest and not of great relevance - unsurprisingly!	Relevance is to the current practice prevailing for patients with T-LOC ringing NHS Direct and shows how these patients are triaged. Also shows the downstream effect e.g. on A &E attendances, GP practice attendances of such triage.
PR	NETSCC, Health Technology Assessment Refere	20	Full	262	3	Similar problems again, but here the upper limits of the CIs for some of the proportions are being reported as exceeding one.	Thank you for your comment. We accept that for some of the studies, the simple formula we used to calculate standard errors was inappropriate (e.g. small sample size). We have now calculated asymmetric confidence intervals for all these data and replotted the graphs on appropriate axes.

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	e 1						
PR	NETSCC, Health Technology Assessment Referee 1	21	Full	General	General	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** In general I did not find a very clear trail from the evidence to the recommendations. Many of the sections start 'There was one low quality study ..', followed by detailed results from that study, but with little discussion of the limitations of the study and the consequent implications.	We have added extensively to the evidence to recommendations sections to address this.
PR	NETSCC, Health Technology Assessment Referee 2	21	Full	10	6	Please make any additional comments you want the NICE Guideline Development Group to see, feel free to use as much or as little space as you wish. ?Suggest Medical assessment Unit/Emergency Department - in certain areas the latter will be more commonly used	We have used the term Emergency Department.
PR	NETSCC, Health Technology Assessment Refere	22	Full	General	General	**3.2 Are any important limitations of the evidence clearly described and discussed?** As mentioned above, I do not in general feel that the implications of weaknesses in study design are followed through to see how they impact on the strength of the recommendations which can be drawn.	We have revised chapter 3 and added extensively to the evidence to recommendations sections to address this.

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	e 1						
PR	NETSCC, Health Technology Assessment Referee 1	23	Full	General	General	**4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.** The report is hugely long and detailed, with to me insufficient emphasis on what parts are supported by strong evidence and far too much detail from the weak studies. How many 'jobbing' clinicians and others are going to take the time to work through all of this?	The full version of the guideline is not really intended for 'jobbing clinicians', who would be well served by the NICE and QRG versions. The full version gives all the details of the evidence synthesis and how the recommendations were derived. We are required to make recommendations to answer all the clinical questions, so have to present all the evidence. Where there is both strong and weak quality evidence the GDG has placed more confidence in the former.
PR	NETSCC, Health Technology Assessment Referee 1	24	Full	General	General	4.2 Please comment on whether the research recommendations, if included, are clear and justified None.	Noted with thanks
PR	NETSCC, Health Technology Assessment	25	Full	General	General	**Please make any additional comments you want the NICE Guideline Development Group to see, feel free to use as much or as little space as you wish.** As discussed above, I think the report is too long and too flat. What parts are robust with strong conclusions and where are the major gaps in the evidence base? I got too	We have revised chapter 3 and added extensively to the evidence to recommendations sections to address this

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	Referee 1					lost in the fine detail to see any obvious 'big picture'.	
PR	NETSCC, Health Technology Assessment Referee 1	26	Full	General	General	The authors have taken on a massive task – maybe too ambitious? In many places there are worrying signs of a lack of methodological input (e.g. in the inappropriate confidence intervals and in the use of correlation to assess agreement), but how could the authors be expected to have access to sufficient time of experienced methodologists to do a really comprehensive synthesis of a large and very flawed evidence base?	Noted. There have been revisions, particularly to chapters 3 and 5
SH	Arrhythmia Alliance	1	Full	General	General	The draft guideline identifies 5 types of T-LOC :- - simple faint (Reflex Syncope) - situational syncope - cardiac syncope - epilepsy - psychogenic blackouts However, those of us working with blackouts patients, and families and relatives, know that the biggest "problem blackout" doesn't quite fit these easy labels. Usually, this type of blackout is due to ***convulsive syncope***, and usually, the syncope is Reflex Syncope. The problem arises from the fact that this blackout doesn't look like, and is not reported as, a simple faint. There is often abrupt T-LOC, there may be injuries, including	Thank you for your comment. The guideline already emphasised that brief seizure activity may occur during syncope. We have modified the text further to emphasise the difference between descriptive terms (such as convulsive syncope) and mechanistic terms (such as vasovagal syncope). Convulsive syncope may be observed during some forms of cardiac syncope and is not confined to a vasovagal (reflex) mechanism. The guideline aims to direct only those with strong features suggesting epilepsy towards neurological assessment, for the reasons that you have highlighted.

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						injuries in the mouth, there may be shaking or jerking of the limbs, (myoclonus), there may be incontinence, the T-LOC may be quite prolonged, and the patient may be drowsy or ill afterwards. All this can occur in Reflex Syncope. Because the blackout appears to be "serious", there may be a search for structural or electrical heart disease, but if nothing is found, patients may easily get labeled with epilepsy and sent immediately to a neurologist. Once there, they often get stuck with a diagnosis of epilepsy and with epilepsy drugs. There could be a problem if all Reflex Syncope is characterized as a simple faint, and it is not made very clear that convulsive features can be seen, but do not imply epilepsy. In other words, it may be a ***"complex faint".*** We know that this happens all to frequently. Indeed, the 2007 All-Party Parliamentary Working Group on Epilepsy in England reported that there were at least 74,000 patients with a misdiagnosis of epilepsy in England alone, and these were patients taking epilepsy drugs. There might be many more with a label of epilepsy hanging over them. I would like to see ***"convulsive syncope"*** added to the list of syncopes, and I believe it will make a contribution to preventing the misdiagnosis of epilepsy.	
SH	Arrhythmia Allianc	2	Full	General	General	I think it would be helpful if the Guideline took the cue from the NSF for Heart Disease Chapter 8, Arrhythmias and Sudden Cardiac Death, 2005, and the 18-Week	This is a clinical guideline giving guidance to clinicians on managing TLoC. How to configure the service is part of implementation and may very locally in different health

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	e					Commissioning Pathway for Blackouts, 2007, and specified Rapid Access Blackouts Triage Clinics for the initial evaluation and triage of blackouts patients after first response, and before specialist referral. These clinics are a very good way of drawing together in one team, all the resources and routines described in the Guideline for management of blackouts patients.	communities. We have been clear in the recommendations the competencies required.
SH	Arrhythmia Alliance	3	Full	General	General	There is no guidance about what should be done for patients suspected to have psychogenic blackouts. I have managed a few of these cases, and many have a tragic history of sexual abuse in childhood or adolescence. Whilst there is little good evidence about what to do and how to help these patients, they are frequently abandoned and discarded by the system because they are labeled as malingering or acting. Detailed history-taking is the key to unraveling their problems, which must surely be the first step. Psychological support and counseling is the minimum that should be offered if psychogenic blackouts are discovered. Despite the fact that there is little good evidence on what to do, I don't think the Guideline should therefore leave a blank space, but should recommend good common-sense measures.	Developing a guideline in the requisite time requires a prioritisation of the scope. We have broadened the diagnostic pathway, adding some information on psychogenic pseudosyncope and PNES. However, we did not have the capacity to fully review the evidence base for this topic – and one small review is included. This relates to diagnostic test accuracy of signs and symptoms for psychogenic pseudosyncope. The view of the GDG is that this subject merits its own guideline and has referred the topic to NICE. We have, however, added a recommendation that health care professionals should consider psychogenic pseudosyncope and PNES if a person has persistent unexplained TLoC.
SH	Arrhythmia Allianc	4	Full	57	6	The term "blackout" is an appropriate term to use interchangeably with T-LOC. Patients, families and neurologists seem to be quite comfortable using it, but	Thank you for your comment. We have emphasised that "blackout" is the description that people may use for their episode of TLoC for exactly the reason that you state. We

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	e					many clinicians are concerned that the correct term, T-LOC, should be agreed and used. However, T-LOC is not used in day-to-day parlance, and is not understood by patients and families. It would be helpful to note in the Guideline that "blackout" is defined in the Oxford English Dictionary as, "a temporary loss of consciousness". I think it would be a good idea to state this and validate the term that patients use.	agree that this is widely understood by people in general and by clinicians of all specialties so we did not feel that it was necessary to quote the Oxford Dictionary specifically.
SH	Arrhythmia Alliance	5	Full	General	General	It is well known that facial pallor is a feature of Reflex Syncope, but many of the clinical studies do not seem to have evaluated the power of this feature to indicate Reflex Syncope. This could be an important omission of the guideline, because it is not included in the analysis of the literature. However, facial pallor occurs in Reflex Syncope because blood is diverted from the skin to the skeletal muscles as a consequence of sympathetic withdrawal. In effect, facial pallor is a physical sign of sympathetic withdrawal in the patient with syncope in the absence of any cardiac or arrhythmic cause. Facial pallor is an important witness statement, and should be mentioned in the guideline.	While we accept that it may be a feature, the evidence demonstrates that this is not a strong predictor.
SH	Association of British Neurologists	1	Full	general	general	This is a much-needed and very comprehensive guideline, well researched and well written.	Noted with thanks

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SH	Association of British Neurologists	2	Full	29	5	**Definitions.** To define TLoC (transient loss of consciousness) as "transient loss of consciousness with complete recovery" is a tautology. Rather than giving this as a definition, it would be better to state that for the purposes of this document, "TLoC" is interpreted as "transient loss of consciousness with complete recovery". The European Society for Cardiology guideline uses the term TLoC to encompass all disorders characterized by self-limited loss of consciousness, irrespective of mechanism[1]). The European Guidelines are well-established and widely-regarded, and NICE should consider adopting this terminology.	Thank you for your comment. We have modified the text to try to provide a clearer definition with a lesser degree of tautology. With regard to adopting the ESC definition, the reference is to the 2009 version. This guideline commenced in 2008. In the previous (2004 p471) version the ESC definition was one of syncope, not TLoC. As the guideline is addressing TLoC for which syncope is one cause, the GDG spent some time early on in development agreeing a definition for the development of the guideline.

[1] Guidelines for the diagnosis and management of syncope (version 2009).The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC). European Heart Journal (2009) 30, 2631–2671.

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SH	Association of British Neurologists	3	Full	29	5	Scope of the Document. The similarity of the document's definition of TLoC to the definition of syncope inevitably leads to an overwhelming emphasis on syncope as the cause of TLoC, with almost no consideration that epilepsy or psychogenic non-epileptic attacks may also present as unexplained TLoC.	The scope was consulted upon published 18 months ago and is the reference upon which the guideline was developed.
SH	Association of British Neurologists	4	Full	General	general	Epilepsy. Whilst appreciating that over-diagnosis (and hence over-treatment) of epilepsy in TLoC cases is more common than its under-diagnosis, epilepsy as a cause of TLoC does nevertheless deserve more consideration within this draft guideline. The document refers to the NICE guidance on epilepsy in adults and children (2004) but this is not sufficient to cover the assessment of patients with epilepsy who present first as TLoC.	We considered how we would address patients who are suspected of having epilepsy and felt we were not is a position to try and rewrite CG20. Once the diagnosis of epilepsy is considered we signpost the epilepsy document.
SH	Association of British Neurologists	5	Full	1.1.5.2.1.2.2.	14 26	Psychogenic non-epileptic seizures commonly present as TLoC and are easily misdiagnosed as syncope or as seizures. The document makes almost no mention of psychogenic seizures as a differential diagnosis of TLoC, and this may lead to the guideline advising unnecessary	Thank you for this point. As a result we have also broadened the diagnostic pathway, adding some information on PNES. The GDG has referred the topic of PNES to NICE to be developed as a guideline in its own right.

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				4.		investigation. There are two examples: 1.1.5.2 line 14 of the draft guideline advises referral of all patients with TLoC to cardiologist, unless it is epileptic seizure, without considering that psychogenic attacks may also present in this way. 1.2.2.4. line 26 refers to the investigation of very frequent TLoC (with ambulatory ECG monitoring) without referring to the common clinical situation where such episodes are psychogenic, and detailed cardiac investigation wasteful or inappropriate.	We have, however, added a recommendation that health care professionals should consider psychogenic pseudosyncope and PNES if a person has persistent unexplained TLoC. The GDG did not feel sufficiently confident in the evidence to make a recommendation for the differential diagnosis of psychogenic forms of syncope at the initial stage and therefore considered this as a second stage diagnosis following investigation for syncope causes. The limited evidence suggests that 'frequent attacks' indicating psychogenic pseudosyncope means many attacks in one day. We have within the guideline indicated appropriate referral pathways that should ensure that specialist consultation is available.
SH	Association of British Neurologists	6	Full	General	general	Neurological investigations. Because the document focuses on syncope, it omits almost any reference to EEG and to CT head scanning in the evaluation of TLoC. EEG. Epilepsy is commonly suspected as a cause of TLoC and although the purist would like to think that EEG can be over-interpreted and so is only for syndrome categorization of definite epilepsy, in fact the EEG can provide additional diagnostic information in cases where the diagnosis is uncertain.	The GDG considered EEG and felt it should not be used in the routine investigation of TLoC, it should only be requested by neurologists as part of the assessment of epilepsy. We also considered CT scanning and felt that it should not be routinely requested in patients suffering a TLoC as long as they had made a full recovery. The conditions listed would most appropriately be investigated by a neurologist as part of specialist further assessment.

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						A guideline on TLoC should also include the indications in such cases for undertaking video EEG monitoring. Brain imaging. Similarly, brain imaging is not considered in the document. Yet, there are many patients with unexplained blackouts (unexplained TLoC), especially if unwitnessed, where brain imaging is important in excluding an intracerebral lesion, either as a cause of epilepsy (space occupying lesion) intermittent hydrocephalus (colloid cyst or Chiari malformation), or intracerebral haemorrhage (aneurysm or AVM).	
SH	Association of British Neurologists	7	Full	11 15 1.2 .1. 1. 99	21 16 28 1	**Lying and standing blood pressure.** Page 11, line 21; page 15, line 16, section 1.2.1.1 line 28; and page 99 (Table). The recommendation to use lying and standing blood pressure measurement in the first assessment of patients with TLoC needs to be clarified. The definition of orthostatic hypotension at 1.1.4.3 line 10 as including "systolic blood pressure falls by at least 20 mm Hg in the first 5 minutes after standing up from a supine position" should also mention the relative absence of associated change in pulse rate during the manoeuvre. On the other hand, patients with reflex (vasovagal) syncope typically show a slight rise in blood pressure on first standing and so this investigation will be unhelpful or even misleading on them.	Thank you for your helpful comments. The guideline's aim is to ensure that people's medical conditions are identified and managed correctly. The text has been modified to make clear that this is not about making a definitive diagnosis. The GDG recognised that a full review of the literature on orthostatic hypotension (including in patients without TLoC) is needed to identify correct definitions for orthostatic hypotension and to consider alternative tests such as tilt testing. We therefore changed the recommendation to describe the orthodox method, but also to say that the person should be referred for further cardiovascular assessment if the person has a suggestive history of OHT that is not confirmed by the simple test. We also revised

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						It is unrealistic to advise clinicians that all patients with syncope must undergo a clinical procedure that takes at least 5 minutes unless there is clear evidence that this is helpful to the diagnosis. Thus, the guideline should give advice on which patients to target for lying and standing blood pressure (i.e. usually elderly people with suspected orthostatic hypotension) and some advice on how to perform the procedure (measurement of pulse and blood pressure lying, followed by measurement of pulse and blood pressure immediately on standing and again after standing for 5 minutes). In other words, the test is worth doing properly and completely in a few selected individuals, but should not be recommended for all patients with TLoC.	recommendation 1.3.1.1 to indicate that not every person with TLoC should have a supine/standing blood pressure test.
SH	Association of British Neurologists	8	Full	general	general	**Improving recognition of convulsive syncope.** It is widely recognised, especially following the work of Lempert et al (1994)[2], that convulsion can be a part of uncomplicated reflex syncope in otherwise healthy individuals. Furthermore, some faints have features that might give the initial impression of an epileptic seizure. Sometimes the onset of syncope can be with little or no warning, there may be limb jerking (which surprised or frightened witnesses may describe as being for much	Thank you for your comment. The guideline already emphasised that brief seizure activity may occur during syncope. We have modified the text further to emphasise the difference between descriptive terms (such as convulsive syncope) and mechanistic terms (such as vasovagal syncope). Convulsive syncope may be observed during some forms of cardiac syncope and is not confined to a vasovagal (reflex) mechanism. The guideline aims to direct only those with strong features suggesting epilepsy

2 Lempert T, Bauer M, Schmidt D. Syncope: a videometric analysis of 56 episodes of transient cerebral hypoxia. Ann Neurol 1994;36:233-237.

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						longer than the fact), injuries including to the mouth, incontinence of urine and even confusion afterwards. NICE have an opportunity to make much more of the diagnostic problem of convulsive syncope, and the associated consequent risk of over diagnosis of epilepsy.	towards neurological assessment, for the reasons that you have highlighted.
SH	Association of British Neurologists	9	Full	1.1.5.127	22 box in algorithm	NICE guidance on epilepsy in adults and children (2004) advises that for suspected epilepsy the person should be seen by a specialist within 2 weeks (not 4 weeks as stated in the document.	We agree that the correct figure is 2 weeks, and have corrected the document.
SH	Association of British Neurologists	10	Full	general	general	The focus of this document is so firmly on syncope that there is a strong case for changing its title to "Syncope in Adults". If NICE are planning to stick with TLoC then the scope of the differential diagnosis and the suggested investigation and management plans will need to be much broader.	This guideline is closely linked with the Epilepsy guideline (CG20) and was commissioned to address some of the gaps in that guideline prior to referral to neurology. We recognise in the consultation version this link was not clear and we have made clearer the scope of the guideline in the introduction. We have also broadened the diagnostic pathway, adding some information on PNES. The GDG has referred the topic of PNES to NICE to be developed as a guideline in its own right. However, this is a diagnostic guideline and therefore does not address management once a diagnosis is made.
SH	Depart	1	Full	Ge	Ge	Thank you for the opportunity to comment on the draft for	Noted with thanks

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	ment of Health			neral	neral	the above clinical guideline. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	
SH	East Midlands Ambulance Service NHS Trust	1	Full	General	General	The full guidelines do not take into account the vital role of the ambulance staff first on scene at a patient suffering a Tloc, it only mentions the transport to hospital and the completed report form. There needs to be provisions for the inclusion of a set format for the ambulance staff to follow, e.g. a set of common questions, the six P's and a flowchart to consider the most effective Referral pathways for treatment. It would be useful to add an inclusion for the ambulance staff to help compile more accurate statistics for patients with TLoc. The ambulance staff are usually the first port of contact both obvious and sometimes accidental findings and therefore need priority inclusion in the guidelines but as with all guidelines, they need to be consistent with levels of knowledge of staff across the ambulance service with the most common being available in small pocket sized flowcharts and bullet point methods.	The GDG recognises and has discussed the vital role ambulance staff play in this condition. People may present, however, to different services, GP's, NHS Direct, ED etc. The guideline is giving guidance to whomever is the first point of contact. Your suggestions for ambulance staff are excellent and we will bring them to the attention of the Implementation Team at NICE.
SH	Epilepsy Action	1	Full	10-11	n/a	We ask the guideline group to add the following to the list of features, one or more present, indicating that referral for assessment by an epilepsy specialist is required. These diagnosis differentials are found in Appendix A of NICE	We agree that these features are appropriate to be considered by a neurologist in the diagnosis of epilepsy, but felt that we should suggest that the patient should be referred on for the diagnosis to be confirmed, rather than

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						Clinical Guideline 20 (the epilepsies). •Sudden falls. •Involuntary jerky movements of limbs whilst awake. •Blank spells. •Unexplained incontinence of urine with loss of awareness, or in sleep. •Odd events occurring in sleep, e.g. fall from bed, jerky movements, automatisms. •Episodes of confused behaviour with impaired awareness, recollection. For identifying possible simple partial seizures specifically, •Epigastric rising sensation. •Déjà vu. •Premonition. •Fear. •Elation, Depression. •De-personalization, derealization. •Inability to understand or express language (written or spoken). •Loss of memory, disorientation. •Olfactory, gustatory, visual, auditory hallucination. •Focal motor or Somatosensory deficit, or positive symptoms (jerking, tingling).	creating a textbook on medical diagnosis. We do refer to CG20, but cannot duplicate their guidance in ours, not least because CG20 is currently being updated. The diagnosis of simple partial seizures is not relevant, as by definition these are not a cause of transient loss of consciousness. SIGN has produced separate guidance on Epilepsy or Scotland and their conclusions are not applicable for the NHS in England and Wales.

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						("Differential diagnosis of epilepsy in adults and children", Appendix A Table 1 - NICE Clinical Guideline 20: The diagnosis and management of the epilepsies in adults and children in primary and secondary care, 2004). Additional indicators of epilepsy can also be found in the SIGN Clinical Guideline for epilepsy (Guideline 70, Section 2). Including these differentials would also be beneficial to reach an accurate diagnosis. If the background of the patient includes: •Head injury. •Alcohol abuse. •Drug abuse. •Prolonged febrile convulsion. •Meningitis. •Encephalitis. •Stroke. •Family history of epilepsy. If the following provoking factors are present: •Sleep deprivation. •Alcohol withdrawal. •Flashing lights. If the any of the following clinical characteristics presented themselves during the attack:	

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						Movements: •Tonic (stiffening) followed by rhythmic jerking •Cyanosis Timing: •Relationship to waking and sleep, clustering with menses If the following clinical characteristics presented themselves after the attack: •*Stereotyped*, brief (seconds) in localisation related epilepsy only. •Taste/smell. •Rising abdominal sensation. •Drowsiness. •Limb aching. •Focal neurological deficit (Todd's paresis). All these differential diagnosis characteristics of epilepsy are listed within Table 1. Available http://www.sign.ac.uk/guidelines/fulltext/70/section2.html	
SH	Epilepsy Action	2	Full	1	Title	Title "Transient loss of consciousness (T-LOC) management in adults". The aim of the Guideline, is "to define the appropriate pathways for the initial assessment of patients with T-LOC and so to derive the correct underlying diagnosis quickly, efficiently, and cost-efficiently, and tailor the management plan to suit their true diagnosis " (page 55). Thus the main goal of the NICE guideline seems to be in the initial	This guideline is closely linked with the Epilepsy guideline (CG20) and was commissioned to address some of the gaps in that guideline prior to referral to neurology. We recognise in the consultation version this link was not clear and we have made clearer the scope of the guideline in the introduction. With regard to psychogenic T-LOC, have also broadened

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
						differential diagnosis and triage of T-LOC. However, the document does not give equal weight to all causes of T-LOC. The emphasis of the document lies very strongly on syncope and in particular on cardiac causes, and other causes receive comparatively little attention. In fact, epilepsy, a rather important form of T-LOC, is only treated to the effect that hints are given for its recognition. Psychogenic T-LOC, another important cause of T-LOC, is hardly dealt with. A simple solution would be to change the title. The title could read something like: initial differential diagnosis and triage of T-LOC with emphasis on detection or exclusion of cardiac syncope It should also be made more clear that the systemic review and critical appraisal deals almost exclusively with diagnosing syncope, but not systematically with treatment of syncope/ T-LOC, although some treatment advices are given. This issue is dealt with shortly (a bit hidden) on page 78. When the guidelines get into the detail of treatment at some points, they run the risk of becoming controversial. It might have been better to say "treatment of syncope - see ES Guideline, treatment of Falls - see NSF for the Elderly, treatment of epilepsy - see NICE Guideline for epilepsy"	the diagnostic pathway, adding some information and a recommendation on psychogenic pseudosyncope and PNES. The GDG has referred the topic of PNES to NICE to be developed as a guideline in its own right We acknowledge your point that some of the advice on managing the condition once a diagnosis is made is beyond the scope of the guideline and the evidence reviews and have therefore removed this to be within the scope.
SH	Epilepsy	3	Full	Gene	Gene	*Convulsive syncope* The Guideline's main focus in dealing with vasovagal	Thank you for your comment. As you say, the guideline already emphasised that brief seizure activity may occur

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	Action			ral	ral	syncope is the simple/ uncomplicated faint. It is mentioned that "myoclonic jerks" may occur, but it could be considered to emphasize that a vasovagal syncope with impressive jerks does not look like or sound like a simple faint at all. There is often abrupt loss of consciousness, there may be injuries, there may be impressive shaking or jerking of the limbs, there may be incontinence, the loss of consciousness may be quite prolonged, and the patient may be drowsy or feel ill afterwards.These patients easily get labelled with epilepsy and sent immediately to a neurologist. Once there, they often get stuck with a diagnosis of epilepsy and with epilepsy drugs. We know that this happens all too frequently. Indeed, the 2007 All-Party Parliamentary Working Group on Epilepsy in England reported that there were at least 74,000 patients with a misdiagnosis of epilepsy in England alone, and these were patients taking epilepsy drugs. There might be many more with a label of epilepsy hanging over them. We would like to see "convulsive syncope" added to the list of syncopes.	during syncope. We have modified the text further to emphasise the difference between descriptive terms (such as convulsive syncope) and mechanistic terms (such as vasovagal syncope). Convulsive syncope may be observed during some forms of cardiac syncope and is not confined to a vasovagal or to a "reflex" mechanism. The guideline aims to direct only those with strong features suggesting epilepsy towards neurological assessment, for the reasons that you have highlighted.
SH	Epilepsy Action	4	Full	General	General	Epilepsy The guidelines do not discuss the use (and abuse) of EEG in the investigation of patients with T-LOC. Many clinicians are still tempted to use EEG as an investigation for all cases of T-LOC, although this test is associated with a high risk of false positive interpretations. The same can be said about the use and abuse of imaging (MRI, CT) in the context of T-LOC. There are several reasonably large studies which describe the yield of EEG	See previous comment. We agree that EEG should not be routinely requested and have modified the Guideline accordingly. We considered imaging and did not feel that we could make a negative recommendation not to scan a patient, but consider that scans would normally be requested as part of further specialist investigation.

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						and MRI in the TLOC setting (for instance the studies by Kotsopoulos and the somewhat dated Australian study by King et al.). The document despite being about T-LOC does not engage very deeply with the diagnosis of epilepsy. The focus seems to be on the differential diagnosis of syncope. Two points, which could be raised in this context, are the delay in the onset of abnormal movements that occurs in NMS and does not occur in epilepsy. Secondly, there is no discussion of the part of the tongue that is bitten in epilepsy versus that which occasionally occurs in NMS. Why use the term bedwetting when incontinence of urine is implied. If this really means that the attack has taken place during the night when asleep then the diagnosis is much more likely to be epilepsy.	The GDG notes the comment about the site of tongue bite, we are aware of this clinical pointer but the evidence we reviewed had much uncertainty around the estimate of the likelihood ratio so we did not feel confident in recommending the specific site rather than general tongue biting, for which there was fairly strong evidence. Likewise, although we agree with the observation that there may be a delay before the onset of abnormal movements in "convulsive syncope" we did not find this in published evidence. Regarding 'bedwetting' - we have reported the signs and symptoms exactly as described in the study. A second study (now included) investigated 'urinary incontinence' as a predictor for epileptic seizures compared with syncope and found no significant difference. This heterogeneity between studies could be caused by differences in study quality or could be differences in terminology - we assume the term 'bedwetting' is more specific (meaning urinary incontinence at night). In view of this uncertainty, we did not include either term as a predictor for epilepsy.
SH	Epilepsy Action	5	Full	General	General	Qualys. NICE is obsessed with QALYS. While these are very important in assessing treatment of mortal diseases they have no relevance in assessing non-mortal conditions. It must be	The use of Quality adjusted life-years (QALYs) as an overall measure of health outcome is consistent with NICE's reference case for economic evaluations. QALYs incorporate both survival gains and improvements in health

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						remembered that the vast majority of patients we see with T-LOC have a non-mortal explanation of their problem. In the light of this fact the committee seems to fail to understand that quite a number of patients who show SND and AVB on ambulatory monitoring are actually showing this because they have had a NMS. So mortality figures cannot be translated from those with intrinsic conduction tissue disease to this group of patients. What really matters here is recurrence for two main reasons: recurrence is very disabling and depressing for the patient and recurrence becomes very expensive when it is repeatedly dealt with by ambulances, A & E and many irrelevant tests such as Brain scans and EEGs.	related quality of life (HRQoL). The economic models developed to inform the guideline incorporate an estimate of the HRQoL improvement that results from treatments which prevent recurrence regardless of whether there is any survival gain. The reduction in resource use that results from treatments which prevent recurrence has also been incorporated in the models. The economic models also incorporate estimates of survival gains where this was considered to be appropriate by the GDG. We accept that the survival gains associated with treating patients with transient AV block during syncope may be lower than the survival gains reported in the Devon Heart Block and Bradycardia Survey (Shaw 1985). We have therefore conducted an additional sensitivity analysis in which we assume no survival gain from treating AV block. Whilst this increased the ICERs, the increase was not sufficient to alter the GDG's conclusions that ambulatory ECG is likely to be cost-effective for people with suspected arrhythmia or unexplained TLoC after the initial assessment.
SH	Epilepsy Action	6	Full	3	9-11	We note and agree the high misdiagnosis in epilepsy and that there is an underlying cardiac cause for much of that misdiagnosis. We are not aware of any evidence that cardiac causes are responsible for all the 20-30% misdiagnoses in epilepsy implied by this statement.	We agree that misdiagnosis rates are high, and note this was also the finding of the All Party Parliamentary Group we looked at this issue. We acknowledge that not all misdiagnosis is due to a cardiac cause, (although many are) and have modified the statement to reflect this.
SH	Epilepsy	7	Full	9	n/a	Incontinence (more common in epilepsy than in non-epileptic seizures!) should be mentioned	The guideline aims to direct only those with strong features of a differential diagnosis of epilepsy compared to syncope

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	Action						towards neurological assessment. In this respect, the literature found heterogeneity between studies (one reporting 'bedwetting' – significant – and the other 'urinary incontinence' – not significant). This heterogeneity could be caused by differences in study quality or could be differences in terminology. In view of this uncertainty, we did not include either term as a predictor for epilepsy relative to syncope, The GDG was not confident in the limited evidence reviewed for psychogenic pseudosyncope to differentiate at the initial stage between psychogenic syncope/PNES and epilepsy or syncope. Therefore, it was preferred to investigate psychogenic TLoC after other tests had been carried out. We have added a recommendation that health care professionals should consider psychogenic pseudosyncope and PNES if a person has persistent unexplained TLoC, and noted that differentiation between PNES and epileptic seizures is complex requiring specialist neurological assessment..
SH	Epilepsy Action	8	Full	10	12	'Seizure activity' can cause much confusion, which can be prevented to using 'jerking movements or another literal description instead.	The GDG felt that it was important to retain the term "seizure activity" as it highlights the potential diagnostic difficulty, but agreed that the description could be expanded to include "jerking movements resembling those seen in epilepsy.

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SH	Epilepsy Action	9	Full	10	29	NICE clinical guideline 20 'The epilepsies' states that a person with suspected epilepsy should be referred to a specialist within two weeks, not four as is stated here.	The reference to 4 weeks was an error and has been corrected.
SH	Epilepsy Action	10	Full	11	n/a	Once more there is 'seizure activity'. Substituting a literal description is clear and cannot confuse anyone.	The GDG felt that it was important to retain the term "seizure activity" as it highlights the potential diagnostic difficulty, but agreed that the description could be expanded to include "jerking movements resembling those seen in epilepsy.
SH	Epilepsy Action	11	Full	11	10	Those who already know which symptoms and signs constitute 'presyncope' will not be confused by this statement, but those who do not, might well interpret the various 'aura sensations of an epileptic seizure as 'presyncope'. A literal description might be better.	We agree that "pre-syncope" needs clearer definition and have altered the statement.
SH	Epilepsy Action	12	Full	11	14	While not intended, some people might read only this introduction and conclude that every patent should receive 'specialist cardiology assessment and diagnosis'. This is particularly important as there is no similar section for epileptic seizures.	Thankyou for your comment. The reason for this emphasis is that the reader is looking at the key recommendations section, which is restricted to a maximum of 10. There is a corresponding section for epileptic seizures in the full set of recommendations (page 18).
SH	Epilepsy Action	13	Full	14	3	Incontinence (more common in epilepsy than in non-epileptic seizures!) should be mentioned.	The guideline aims to direct only those with strong features of a differential diagnosis of epilepsy compared to syncope towards neurological assessment. In this respect, the literature found heterogeneity between studies (one reporting 'bedwetting' – significant – and the other 'urinary incontinence' – not significant). This heterogeneity could be

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							caused by differences in study quality or could be differences in terminology. In view of this uncertainty, we did not include either term as a predictor for epilepsy relative to syncope, The GDG was not confident in the limited evidence reviewed for psychogenic pseudosyncope to differentiate at the initial stage between psychogenic syncope/PNES and epilepsy or syncope. Therefore, it was preferred to investigate psychogenic TLoC after other tests had been carried out. We have added a recommendation that health care professionals should consider psychogenic pseudosyncope and PNES if a person has persistent unexplained TLoC, and noted that differentiation between PNES and epileptic seizures is complex requiring specialist neurological assessment..
SH	Epilepsy Action	14	Full	17	11	'Seizure activity' is potentially misleading. We would like to suggest "repetitive myoclonic jerking"	The GDG felt that it was important to retain the term "seizure activity" as it highlights the potential diagnostic difficulty, but agreed that the description could be expanded to include "jerking movements resembling those seen in epilepsy.
SH	Epilepsy Action	15	Full	55	7	"which are probably the most common. Cardiovascular disorders and in particular reflex syncope are by far the most common cause of TLOC in the	We agree

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						population, which you seem to refer to since you say it occurs in 50% of the population. "Just as an example the frequency of epileptic seizures in the population in the young is about 1%, of reflex syncope about 30%	
SH	Epilepsy Action	16	Full	94	8,11,16	First mention of "psychogenic nonepileptic seizures" (PNES)– called "psychogenic seizures" in the first part of the document. The document should use one term. The most commonly used term in the UK is "nonepileptic attack disorder". Alternatively, the document could use the term "dissociative seizures" used in the ICD-10.	The GDG agreed on the term PNES and have added this to the glossary.
SH	Epilepsy Action	17	Full	97	n/a	**3. Eye witness account** *Comment:* Information about myoclonic jerks, eyes open vs closed etc could be included	The section referred to in the comment contains the results of the diagnostic simulation, which was used to inform GDG discussions. This is a record of what was said in this simulation and so cannot be edited or added to retrospectively. We have now moved this section to Appendix D5.
SH	Epilepsy Action	18	Full	98	n/a	**4. Post T-LOC** **-** Were there prolonged symptoms . Epilepsy more likely to have post symptoms. *Commen:* prolonged symptoms are not defined. Syncope can have very prolonged symptoms of weakness and tendency to faint.	The section referred to in the comment contains the results of the diagnostic simulation, which was used to inform GDG discussions. This is a record of what was said in this simulation and so cannot be edited or added to retrospectively. We have now moved this section to Appendix D5.
SH	Medtronic Ltd	1	Full	General	General	Medtronic welcomes the clinical guidance for Transient Loss of Consciousness (TLoC) and particularly welcomes the clarity and recommendation that the guidance provides on the usage of Implantable Loop Recorders (ILRs) for the management of these patients. We would	Noted with thanks

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						like to applaud the tremendous efforts and work of those who prepared this document; very comprehensive indeed.	
SH	Medtronic Ltd	2	Full	General	General	The guidance adopts the term IER (Implantable Event Recorder) instead of ILR (Implantable/Insertable Loop Recorder). From a consistency standpoint, the ICD-9 procedure terminology (37.79) refers to these devices as ILRs and "ILR" is also used in the recent ESC Syncope Guidelines (Moya 2009) and the recent EHRA Position Paper (Brignole 2009). Please also note that the Moya 2009 publication defines "Event Recorders" as external devices which are applied by the patient when symptoms occur. It also states that "Whereas these types of recorders [Event Recorders] can be useful in the investigation of patients with palpitations, they have no role in the evaluation of syncope" (Page 19, Section 2.2.3.3, Moya 2009). In addition, the AHA/ACCF Scientific Statement on the Investigation of Syncope also defines "Event Recorders" as external devices which can be used for a short time by a single patient and are patient triggered (Strickberger 2006). To our perception, "Event Recorder" as a term tends to refer to devices without an automatic function; i.e only patient activated events can be stored.	The term Loop Recorder originated when it was an external device using a loop of magnetic tape. It has been clarified in the glossary that this may be an alternative term.

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						To avoid confusion in the implementation phase of the guidance we would suggest using the term ILR instead of IER.	
SH	Medtronic Ltd	3	Appendix C1	1	1 (Question 1)	In response to the research question, Medtronic has been running an international prospective registry on the usage of ILR over the last years (known as the PICTURE Registry) which may provide hints to this. Specifically: 1- PICTURE recorded the number of first TLoC recurrences (in an Unexplained TLoC population) and time-to-diagnosis of the people who eventually got diagnosed. These could be used to approximate the incidence of new TLoC episodes in this patient population. 2- PICTURE also recorded specifically arrhythmia-related diagnoses made and the therapy received afterwards. This could allow approximating not only the prevalence of underlying TLoC causes in the Unexplained TLoC population but also estimation on the prevalence of exact arrhythmia types (bradyarrhythmia etc.). PICTURE data has been provided to the NICE TLoC Guidance Development Group both on a "Commercial" and "Academic" In-Confidence basis.	Thank you for sending us your preliminary results. This study has been reviewed and is an unpublished study reporting preliminary data. We believe it reinforces our conclusions and will include it in the update of this guideline.
SH	Medtronic Ltd	4	Full	264	16	Indeed, EaSyAS (Farwell 2004 and Farwell 2006) did document a significant number of patients not being able to capture the ECG during their first TLoC recurrence with	Thank you for your comment. We have added a sentence to the evidence to recommendations section.

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						their ILR. The authors attributed that to two factors: (a) failure to manually activate the device and (b) delay between recurrent TLoC and ILR interrogation allowing for captured events being overwritten by data captured after the recurrent TLoC. We believe it is important to note here that EaSyAS used a previous generation ILR (Reveal® Plus). Current ILRs have overcome technical limitations that possible played an important role in EaSyAS. Specifically: 1- Currently available ILRs employ segmentation of the device memory between manually and automatically captured episodes. Furthermore, newer devices will not overwrite automatically captured arrhythmias of one type with automatic recordings of another type. In this way, patient's overuse of the manual capture function will not overwrite automatic recordings and the likelihood of an automatically captured event during a TLoC becoming overwritten by similar arrhythmias outside the TLoC is low. 2- Recent publications (e.g. Brignole 2008, Hindricks 2010) show that the algorithms in some ILRs (Reveal® DX and Reveal® XT) have been significantly improved compared to the older generation. 3- Some available ILRs also allow for a copy of the device memory to be transmitted electronically from the patient's	

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						home via a tele-monitoring system (CareLink®). When this transmission successfully completes, the recordings are permanently stored in a secure server and become available only to the patient's physician. This ensures that any overwrites – no matter how unlikely – do not negatively impact the ability of the physician to diagnose. The PICTURE Registry (detailed in our previous comment) has also shown a substantially increased rate of 'Successful ECG recording at Time of TLoC' compared to EaSyAS and, as detailed in the PICTURE document, included a substantial percentage of newer devices.	
SH	Medtronic Ltd	5	Full	331	26	Indeed, including the injury associated costs of recurrent TLoC in your economic analysis is key for the appropriate estimation of the cost-effectiveness of TLoC diagnostics. Perhaps, only relying on TLoC-themed HRG codes for this cost is underestimating the costs of TLoC recurrence. For example, would a patient suffering a major injury after a TLoC and was admitted subsequently to an inpatient ward for injury treatment be grouped under a "Syncope or Collapse" HRG? If not, then important costs may be left out of the evaluation. We would like to point out two relevant publications to this point.	Having considered Bartolleti 2008, we cannot see how the figure of 24.7% risk of minor injury requiring hospitalisation has been arrived at. In Bartoletti 2008, trauma was defined as any physical injury secondary to TLOC which was clinically relevant enough to be mentioned in the patients' clinical records. The study doesn't report what proportion of patients who had trauma were hospitalised. Only 2.3% of those presenting with TLoC had a severe head trauma. Therefore the costs of major head injuries cited from Morris 2008 are not likely to be applicable to the majority of patients experiencing TLoC. The NHS costs associated with recurrence have been captured within the economic models using estimates from the NHS reference costs. Sensitivity analyses found that

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						1- Bartoletti 2008 looked at the type and body location impacted by a TLoC associated injury after a TLoC. This registry reported 24.7% risk of minor injury requiring hospitalisation after a TLoC and 4.8% risk of major trauma. Furthermore, according to this registry, 73.6% of injuries occur in the head. 2- Morris 2008 looked at the UK NHS costs of major head injuries. The average cost of a traumatic brain injury after a fall less than 2m was found to be £11,412.	alternative assumptions using higher admission rates did not significantly alter the cost-effectiveness.
SH	Medtronic Ltd	6	Full	387	27	On the concept of this economic analysis we would like to point out some differences between today's environment and the one in ISSUE-2 (Brignole 2006), which was used for this evaluation. Please note that ISSUE-2 used the Reveal® Plus and not the currently available devices Reveal® DX and Reveal® XT. 1- Reveal® Plus had a battery life of 14 months while the current Reveal® DX and Reveal® XT devices have a battery life of three years. This could mean that if ISSUE-2 had employed the new devices all patients implanted with an ILR would have fainted within a 3 year time period (as the Kaplan Meyer curves of Figure 3 on Page 1089 of Brignole 2006 suggest). Even assuming the same rate of successful ECG recording after the TLoC, a significant percentage of those would have received a diagnosis. This could improve the number of patients diagnosed by	Thank you for your comments. Each point is responded to as numbered. 1) The GDG have considered the evidence that is currently available. Whilst this may relate to older devices it is not possible to know whether newer devices are more clinically effective until studies reporting the use of these newer devices are published. We do not agree that the Kaplan Meir curves in Figure 3 of Brignole 2006 suggest that all patients would have fainted within a 3 year time period. If one fits a Weibull survival curve to the data in Figure 3 [S(t)= exp(-0.013 x t ^ 0.571)] and extrapolates survival to 3 years, this gives a 47%.risk of remaining syncope free at 3 years. 2) The relevance of Baroletti 2008 and Morris 2008 has been discussed above (see response to comment 5 from

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						an ILR substantially and alter the results of the evaluation. 2- Same as for the other economic analysis conducted as part of the guidance development process, perhaps the costs of recurrent TLoC were underestimated here as well. We would like to point out again to the Bartoletti 2008 and Morris 2008 publications, as well as the Brignole 2006 ISSUE-2 publication (Page 1088, Table 1) which seems to report higher figures than Bartoletti 2008 for TLoC-associated injuries. 3- It is more appropriate to extrapolate outcomes to patient lifetime instead of the duration of ISSUE-2 for the basecase scenario. As noticed in the Full Guidance on Page 390 and Table 35, the ILR ICER vs. TTT seems to improve as the timeframe of the analysis gets longer and the benefits of ILR-guided diagnosis and treatment are allowed to materialise. In conclusion, improvements in the battery life of the currently commercially available devices and the extension of outcomes accrual to patient expected lifetime may put the ILR vs. TTT ICER below the accepted Cost-Effectiveness threshold. Generally, however, we agree with the committee's decision to contrast the results of this analysis with the limitations of TTT as a TLoC diagnostic tool (as also	this stakeholder) 3) The diagnostic outcomes have been modelled using the maximum follow-up available from the diagnostic studies. The model extrapolates post diagnostic outcomes, such as treatment costs and benefits, beyond the duration of the diagnostic studies. The timeframes used to capture post diagnostic outcomes reflect the approach taken in the previous NICE technology appraisals for ICDs and dual-chamber pacing (TA88 & TA96) As discussed in section 6.7.5 of the full guideline, the GDG did not consider the implantable event recorder, IER, (referred to as "ILR" by this stakeholder) to be cost-effective compared to tilt testing when used to direct pacing in patients with vasovagal syncope and highly frequent episodes.

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						suggested in the recent editorial Petkar 2008).	
SH	Medtronic Ltd	7	Full	General	General	Please find listed here references to all papers referred to above that are not referenced by the current version of the full NICE TLoC Guidance. References are provided in order of use in the comments above: 1. Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, et al. Guidelines for the diagnosis and management of syncope (version 2009): the Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC). Eur Heart J 2009;30(21):2631-71. 2. Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, et al. Indications for the use of diagnostic implantable and external ECG loop recorders. Europace 2009;11(5):671-87. 3. Strickberger SA, Benson DW, Biaggioni I, Callans DJ, Cohen MI, Ellenbogen KA, et al. AHA/ACCF Scientific Statement on the evaluation of syncope: from the American Heart Association Councils on Clinical Cardiology, Cardiovascular Nursing, Cardiovascular Disease in the Young, and Stroke, and the Quality of Care and Outcomes Research Interdisciplinary Working Group; and the American College of Cardiology Foundation: in collaboration with the Heart Rhythm Society: endorsed by the American Autonomic Society. Circulation 2006;113(2):316-27.	Thank you for the additional papers. The Moya 2009 paper is already included as a reference We have added information from the Bartoletti 2008 reference to the evidence to recommendations section on red flags.

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						4. Brignole M, Bellardine Black CL, Thomsen PE, Sutton R, Moya A, Stadler RW, et al. Improved arrhythmia detection in implantable loop recorders. J Cardiovasc Electrophysiol 2008;19(9):928-34. 5. Hindricks G, Pokushalov E, Urban L, Taborsky M, Kuck KH, Lebedev D, et al. Performance of a new Leadless Implantable Cardiac Monitor in Detecting and Quantifying Atrial Fibrillation - Results of the XPECT Trial. Circ Arrhythm Electrophysiol. 6. Bartoletti A, Fabiani P, Bagnoli L, Cappelletti C, Cappellini M, Nappini G, et al. Physical injuries caused by a transient loss of consciousness: main clinical characteristics of patients and diagnostic contribution of carotid sinus massage. Eur Heart J 2008;29(5):618-24. 7. Morris S, Ridley S, Lecky FE, Munro V, Christensen MC. Determinants of hospital costs associated with traumatic brain injury in England and Wales. Anaesthesia 2008;63(5):499-508. 8. Petkar S, Fitzpatrick A. Tilt-table testing: transient loss of consciousness discriminator or epiphenomenon? Europace 2008;10(6):747-50.	
SH	National Public Health Service for Wales	1	Full	General	General	The National Public Health Service for Wales (now part of Public Health Wales NHS Trust), will not be participating in this consultation.	Noted with thanks

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SH	National Society for Epilepsy	1	NICE	General	General	We welcome a unified approach towards the assessment of patients who have experienced transient loss of consciousness. Our own audits, and published studies suggest that up to 2% of A&E assessments may relate to patients who have lost consciousness. A proportion of patients who present with TLoC may have cardiological or neurological conditions that warrant urgent assessment. Many dangerous medical conditions or complications of medical treatment may also present with transient loss of consciousness. On the other hand, a number of people with benign faints/syncope will inevitably be seen in this pathway. The formulation of a care pathway to assess and manage TLoC represents a significant opportunity: NICE guidelines are authoritative and widely read. They have a major and enduring impact on how services are delivered in England and beyond. Those producing NICE guidelines have great responsibility - as once guidelines are established, alternative models are more difficult to test and deploy. We feel the guideline as it stands has considerable room for improvement and in particular would benefit from greater expression of a wide range of neurological issues.	Thank you for your comments. The GDG discussed your comment that only TLoC with a cardiological basis warrants "emergency assessment". Their view was that many of the serious neurological conditions to which you refer, would not fall within the guideline's definition of a TLoC – that is that full consciousness was regained. However, as clinicians reading the guideline, may not recognise this distinction another recommendation has been added in the 'red flags' regarding people who do not regain full consciousness. The GDG endorses greater collaboration between the specialities such as joint cardiology/neurology clinics but this is beyond the scope of the guideline. We will raise this with the NICE implementation team.

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						The current version is dominated by consideration of cardiological issues. Even with careful analysis, the reader is left with the impression that only TLoC with a cardiological basis warrants "emergency assessment". Furthermore, there seems to be little emphasis on the importance of liaison between relevant specialists at all points in the care pathway. We feel that adherence to the guideline as it stands would leave unacceptable delays in diagnosis and treatment of potentially life-threatening conditions (such as raised intra-cranial pressure, cerebrovascular events or intra-cranial lesions, all of which may manifest with seizures or transient impairment or loss of consciousness). We feel the solution to the problem of inappropriate management of TLoC lies with greater collaboration between relevant specialists – in particular with neurologists and cardiologists working more closely together throughout the care pathway to determine best management for patients.	
SH	National Society for Epilepsy	2	NICE	General	General	We feel the role of urgent blood work and neuro-imaging is given too little prominence	The GDG discussed the addition of red flags for non-epileptic neurological conditions. It was their view that many of the serious neurological conditions, would not fall within the guideline's definition of a TLoC – that is that full consciousness was regained.

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							People entering the pathway with a TLoC may have simply fainted or they may be seriously ill. Therefore it is difficult to prescribe a strict protocol for the initial assessment particularly as we have had criticism that we are over investigating many. . We have however modified this recommendation to stress that investigations need to be tailored to the person's history.
SH	National Society for Epilepsy	3	NICE	General	General	The guideline fails to recognise the phenomenon of ictal arrhythmia and autonomic disturbance - which may occur either ictally or post-ictally. Syncope, arrhythmia and seizures can (and often do) occur in the same patient. Sudden Unexpected Death in Epilepsy (SUDEP) is the cause of 600 deaths in the UK per year and may be mechanistically related to SAD – but is not mentioned.	We acknowledge that the phenomenon of ictal arrhythmia is problematic. These patients would probably be identified as experiencing an epileptic seizure, unless the arrhythmia was detected on prolonged monitoring. As the underlying condition is one of epilepsy this is really a issue for the Epilepsy guideline CG20.
SH	National Society for Epilepsy	4	NICE	General	General	The guideline fails to describe how prolonged reflex anoxic seizures may be associated with correspondingly longer periods of confusion	The GDG felt that we should provide indications to help clinicians make the initial diagnostic distinctions with reasonable confidence. Trying to distinguish between brief reflex anoxic seizures and prolonged ones introduces an unnecessary complication, not least because witnesses are often unreliable in estimating the length in time of an event. The GDG did not wish to introduce unnecessary potential complications.
SH	National Societ	5	NICE	3	4	Determining whether there has been "complete" recovery can be clinically challenging and is part of the diagnostic dilemma. We are not certain how useful this aspect of	Thank you for your comments. The definition has been modified in the light of your comments and those of others to try to provide greater clarity. Nevertheless it is

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	y for Epilepsy					the definition is ex ante.	impossible to get away from the inclusion of full recovery in the definition. This guideline does not apply to anyone who has a residual neurological deficit or who remains unconscious at the time of assessment
SH	National Society for Epilepsy	6	NICE	3	7	In an acute medical setting, drug/toxins, metabolic causes (including hypoglycaemia) and a number of intracranial causes must all be considered when dealing with a patient who has temporarily lost consciousness – particularly in the numerous cases where a full or reliable history/witness account is unavailable.	Thank you for this comment, we have amended the recommendation and given these as examples.
SH	National Society for Epilepsy	7	NICE	3	9	The statement that "20-30% of people thought to have epilepsy have an underlying cardiac cause..." is not evidenced and is a significant over-estimate compared with published literature.	The introduction has been revised substantially and this has been removed.
SH	National Society for Epilepsy	8	NICE	3	22	Many would argue that the problem is not the lack of a clear pathway: based on the reasonable assumption that however carefully written a guideline is, many patients with neurological problems will be seen by cardiologists (and vice versa) – the solution lies with facilitating liaison between different specialists at all points in the care pathway, and awareness that diagnosis should constantly be reviewed.	The GDG agrees that joined up services would address many of the issues, that is what we are trying to encourage, we are hopeful that this guideline, combined with CG20 may in future help integrate pathways, but we were unable to do this at this stage, within our current scope.
SH	Nationa	9	NIC	4	25-	In virtually all instances, provision of information to third	This is standard text in all NICE guidelines. It makes it

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	l Society for Epilepsy		E		26	parties should only be with the patient's consent. Many people work and spend considerable time at a place of work: work colleagues/occupational health should also be considered	clear that information should be given with the patient's consent.
SH	National Society for Epilepsy	10	NICE	5	5	The list beginning "circumstances.." is only a small part of the information that should be acquired. Key omissions include medical history, drug history, use of alcohol/illicit drugs, concurrent illness etc. Although these issues are touched on later in the guideline, the utility of the list provided is questioned. In particular, we find information about behaviour and activities in the period up to 24 hours before an event can be very relevant in relation to a neurological history - in addition to the more traditionally regarded triggers (e.g. sleep deprivation, alcohol excess, drug use etc.). Head injuries occurring before this point may also be relevant – subdural haematoma may classically present with fluctuating level of consciousness.	We are required by NICE to select ten recommendations as Key Priorities for Implementation. These recommendations are taken out of context. If you refer to the full set of recommendations you will find a recommendation that starts 'Asses and Record' where many of the items in your list are included. It has been amended to give examples. Many of the triggers and neurological history relate to making the diagnosis of epilepsy which is beyond the scope of this guideline. The key aim for this guideline is good signposting to correct referral pathways.
SH	National Society for Epilepsy	11	NICE	5	23	It appears that only patients with a potential cardiac cause for TLoC are regarded as "emergencies" in the draft guideline. This is clearly wrong. We argue that anyone with significant neurological symptoms or signs may also require emergency assessment. For example, a patient who has new or ongoing neurological symptoms such as	The people who you suggest have not had a TLoC, that is, they are unlikely to have a lost of consciousness and fully re-gained consciousness and therefore are outside the scope of the guideline. We have however added a recommendation to advise clinicians to consider other conditions, if patients do not fully regain consciousness.

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						headache, weakness or sensory disturbance, gait disorder, visual disturbance or mood alteration should also be regarded as a medical emergency. Patients with enduring pyrexia or neurological signs who have lost consciousness should also be regarded as emergencies. Certain patients (such as those who are immune compromised, who have suffered head injuries, or are anti-coagulated) may be within particularly high-risk groups. It is likely that many of these patients will require urgent imaging	
SH	National Society for Epilepsy	12	NICE	5	20	We would argue that routine SO2, full blood count, biochemical screen, glucose and calcium are also essential when assessing the patient who has lost consciousness.	People entering the pathway with a TLoC may have simply fainted or they may be seriously ill. Therefore it is difficult to prescribe a strict protocol for the initial assessment particularly as we have had criticism that we are over investigating many. . We have however modified this recommendation to stress that assessment and investigations need to be tailored to the person's history and have given some examples. .
SH	National Society for Epilepsy	13	NICE	6	22	We do not understand the use of the word "strongly" in this context. The term is ambiguous and may lead to patients with epilepsy being diverted away from first seizure clinics.	The problem is that too many are labelled with epilepsy. Those that do have it should be picked up later.
SH	Nationa	1	NIC	6	27-	This list of potential features of seizure activity is very	We do not intend to provide a system to describe seizures,

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	l Society for Epilepsy	4	E		32	limited and excludes a wide range of manifestations of both partial and generalised seizure activity. We do not recognise the system used to describe seizures and this section would benefit from reworking. Our specific comments are that only two types of partial seizure are listed. An epigastric rising sensation is the most common, but also fear, olfactory, gustatory, visual, auditory phenomena, disturbance of language, affect, motor or somato-sensory symptoms. It should be noted that generalised seizures may be preceded by absences and myoclonic jerks.	and were not aware that we had done so. The list of features that we suggest may be helpful in identifying epilepsy has been taken from the literature.
SH	National Society for Epilepsy	15	NICE	7	7	Dizziness or fear can be a manifestation of a partial seizure, and may often be confused with pre-syncope. Sweating (and other autonomic features) may be a manifestation of both partial and generalised seizures and should not be regarded as features that exclude seizures.	The GDG acknowledges that epileptic seizures can have many manifestations, but aim to provide indications to help clinicians make initial diagnostic distinctions with reasonable confidence, acknowledging that the subsequent initial specialist assessment may revise the diagnosis, we do not expect that the first assessment will always provide the final definitive diagnosis.
SH	National Society for Epilepsy	16	NICE	7	3	The possibility of ictal arrhythmia/bradycardia appears not to have been considered but should be included in a guideline about TLoC (see point 3 above)	This has been added as a recommendation in the section 'If the diagnosis remains unclear'
SH	Nationa	1	NIC	7	3	Epilepsy is defined by two or more epileptic seizures and	The aim at this point is not to make a diagnosis but to refer

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	l Society for Epilepsy	7	E			the term should not be considered in this context	to the correct speciality. It is clear in the wording.
SH	National Society for Epilepsy	18	NICE	10	4-29	See point 10 above	See response to point 10
SH	National Society for Epilepsy	19	NICE	12	16-29	See point 11 above	See response to point 11
SH	National Society for Epilepsy	20	NICE	14	13-29	See point 13 and 14 above	See responses to points 13 & 14 above.

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SH	National Society for Epilepsy	21	NICE	11	7-18	See point 12 above	See response to point 12
SH	National Society for Epilepsy	22	NICE	24	17	We do not understand the statement "the prevalence of syncope in the UK.. is... 25%". Lifetime incidence is probably in this region, but prevalence is considerably less	The lifetime prevalence is around 25% . Incidence is reported at around 6 per 1000 person years [ESC Guidelines Update 2004]
SH	National Society for Epilepsy	23	NICE	34	18	It is more correct to say, "Deja vu may be a manifestation of a partial seizure" (rather than "occurring immediately before an epileptic seizure)	We agree and have changed this.
SH	National Society for Epilepsy	24	NICE	35	6	Jamais vu may also be a manifestation of a partial seizure	We agree that jamais vu may be a manifestation of a partial seizure, but this is a rare symptom, and we wish to keep the document as simple as possible.

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SH	National Society for Epilepsy	25	NICE	35	22	It is not appropriate to try to distinguish between 'aura' and 'prodrome' in terms of "prominence" or duration. Aura is a term commonly used to describe partial seizures (or sometimes pre-migrainous symptoms), which may be prolonged and/or intense.	The term "aura means a "puff of wind" and implies a brief sensation, we feel that it is appropriate to distinguish this from the meaning of "prodrome" which we considered to be more prolonged. We have modified the definition in the full guideline.
SH	National Society for Epilepsy	26	NICE	34	1	This Glossary is dominated by terms relating to cardiology. A simple statistic: i.e.16+ cardiological terms included vs. just 2 terms used in epilepsy. Together with gross factual errors ("20-30% of people thought to have epilepsy have an underlying cardiac cause.."), and several other errors of definition or inclusion/exclusion, the impression is created of a guideline that offers too little recognition of neurological emergencies or related epileptic seizures.	We note your views but feel that we have tried to provide a balanced guide to aid clinicians in the initial assessment of individuals who suffer transient loss of consciousness. We have modified the statement regarding misdiagnosis.
SH	National Society for Epilepsy	27	NICE	37	1-2	These figures summarise the care pathway described in the draft guideline: our concerns about this guideline are therefore applicable to the diagram. In particular the lack of reference to need for urgent blood testing or neuro-imaging in appropriate patients is a matter of great concern. We do not agree that Box E is useful in this context	This has been changed to reflect the guideline recommendation changes
SH	Primary Care Cardiovascul	1	NICE	9	11	We suggest that the order is reversed to read "hypotensive response and/or reflex bradycardia" as a hypotensive response is much more common.	Thank you for point this out - it has been changed.

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	ar Society						
SH	Primary Care Cardiovascular Society	2	NICE	10	13	We would suggest that it is worth checking whether urinary and faecal incontinence have occurred in addition to tongue biting or injury. It is perhaps worth pointing out that incontinence can occur in patients with profound bradycardia / asystole in the context of neurally mediated syncope	The evidence did not show that incontinence was a good differentiator.The guideline aims to direct only those with strong features suggesting epilepsy towards neurological assessment.
SH	Primary Care Cardiovascular Society	3	NICE	12	16	While we would agree that anyone with a threatening ECG abnormality should be categorised as high risk, the list of ECG abnormalities on Page 11 does not appear to differentiate people whose ECG shows first degree heart block or partial right bundle branch block (both being degrees of heart block as per Page 11, Line 26) from people with trifascicular block or Mobitz type 2 AV block. This raises the potential for increasing the number of people being referred urgently (and perhaps unnecessarily) while also (and perhaps more importantly) diluting the perceived significance of the more threatening ECG abnormalities.	This has been reviewed and strengthened.
SH	Primary Care Cardiovascular	4	NICE	12	23	While agreeing that anyone older than 65 should be rapidly assessed, we are not clear that there is sufficient evidence that all patients in this group should be admitted rather than be given an urgent specialist appointment (e.g. within 7 or 14 days). Many of our patients who are admitted in	Thank you for pointing this out. We have clarified the wording so that it is clear that it is an assessment within 24 hours but not necessarily admitted. We have deleted the general advice to admit.

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	Society					this context sit on wards for days on end awaiting investigations.	
SH	Primary Care Cardiovascular Society	5	NICE	12	23	While anyone with an ejection systolic murmur that has not been assessed should be referred urgently, we are concerned that urgent admission for a patient with e.g. mild to moderate MR may not be appropriate. This may lead to an increase in unnecessary admissions without any tangible benefit for the patient.	We have clarified the wording so that it is clear that it is an assessment within 24 hours but not necessarily admitted leaving some clinical judgement. We have deleted the general advice to admit.
SH	Primary Care Cardiovascular Society	6	NICE	13	3	Line 3 works fine if the word "uncomplicated" is also inserted in brackets before "vasovagal"). Not all vasovagal syncope is uncomplicated e.g. if associated with profound bradycardia or prolonged asystole or with significant injury.	Thank you, this has been changed.
SH	Primary Care Cardiovascular Society	7	NICE	13	9 & 12	We would argue that there is a difference between someone having a simple or "uncomplicated faint" and a person who loses consciousness while in a seated position. The mechanism might be vasovagal in both but the latter should not be deemed "uncomplicated" in the usual sense of the word as this presentation may have significant implications for the patient e.g. issues re driving depending on the full details.	We have clarified this by adding - 'does not usually occur when sitting or lying'.

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SH	Primary Care Cardiovascular Society	8	NICE	15	7	We would strongly encourage you to reconsider this line which we believe should read "Referral for specialist cardiology assessment or specialist syncope service assessment – all other people with TLoC". There are many services around the U.K. that have been developed specifically for the assessment and management of people with TLoC that n initial assessment does not seem to have been caused by epilepsy. Many of these include clinicians with significant cardiology training. Clearly they should all have very close links with their cardiology and neurology colleagues. It would be an incomplete guideline that did not include them.	This has been added
SH	Primary Care Cardiovascular Society	9	NICE	15	22	The optimal assessment of orthostatic hypotension includes beat to beat blood pressure monitoring, which would be a standard test in most syncope units.	We agree. The aim of the guideline to encourage appropriate referral which would be to a syncope unit where they exist. We have been clear that it is a specialist cardiac referral rather than a referral to cardiology.
SH	Primary Care Cardiovascular Society	10	NICE	16	15	There does not appear to be a particular reason for the words "and do not offer a tilt test" here in the same way as there would be no reason to suggest that a CT of head should not be done. If the clinical picture is of an arrhythmic cause, then neither a tilt test or a CT head should be done and it is odd that the guideline should specifically mention tilt testing here.	We discuss in the evidence to recommendations section the evidence for why a tilt test should not be used in this population – which it clearly has been, at least in research studies.

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SH	Primary Care Cardiovascular Society	11	NICE	16	18-29	We agree that 24 hour Holter monitors are overused and rarely provide a diagnosis in the TLoC setting. Many hospitals will provide a 5 day Holter monitor for a patient who has episodes of TLoC every few days. We are not clear that limiting to 48 hours is in the patients' best interest. Most of our patients, who have episodes of TLoC every 3-4 weeks, would not wish to have an implantable loop recorder unless they had tried an external loop recorder first for approx this period of time.	The less frequent the symptoms the more an implantable becomes appropriate but we have added patient preference
SH	Primary Care Cardiovascular Society	12	NICE	17	3-10	We would agree that tilt testing is not necessary for people with a clear diagnosis of uncomplicated neurally mediated syncope. It may however be beneficial in some patients with complicated neurally mediated syncope or to check for a profound cardioinhibitory response as described. It may also be useful for some people in whom the diagnosis is not clear e.g. in some patients for whom there is a history of jerking limb movements but epilepsy is not felt to be the diagnosis.	We agree refer to next recommendation
SH	Primary Care Cardiovascular Society	13	NICE	17	22-25	We do not believe that this advice represents best practice and would respectfully request that this is reconsidered.	This is been based on the evidence. We have reworded to clarify

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SH	Royal College of Nursing	1	General	General	General	The Royal College of Nursing welcomes the opportunity to comment on this draft guideline. The document is comprehensive.	Noted with thanks
SH	Royal College of Nursing	2	NICE	5	Lines 7 - 15	Key priorities for implementation – Initial assessment and diagnosis: "Whether any urinary incontinence occurred during the event" should be added to the checklist	The evidence did not show that incontinence was ~~not~~ a good differentiator.The guideline aims to direct only those with strong features suggesting epilepsy towards neurological assessment.
SH	Royal College of Nursing	3	NICE	5	14	Key priorities for implementation – Initial assessment and diagnosis: Also it needs to clarify what is meant by time to recovery – does this mean time taken to regain consciousness or time taken to get back to normal – both are important and may not necessarily be the same thing	Thank you for this comment we have clarified that recovery is regaining consciousness.
SH	Royal College of Nursing	4	NICE	5	general	Should there be mention of drug therapy or family history, previous unreported episodes and any current stress mediators as part of the initial assessment process?	The recommendation that starts 'Assess and Record' includes previous episodes, medications, family history and medical history. It has been amended to give examples.
SH	Royal	5	NIC	6	21	Key priorities for implementation – Initial assessment and	The guideline gives advice on investigations and

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	College of Nursing		E			diagnosis: Referral process – needs to reinforce the involvement of epilepsy nurse specialists within emergency departments, they could have a very valuable advisory role to play here.	management, it does not make reference to particular professions.
SH	Royal College of Nursing	6	NICE	1.1.5.1	17	Predictive factors indicating need for referral to a specialist in epilepsy: NICE guideline recommends this assessment takes place within 2 weeks not 4	The reference to 4 weeks was an error and has been corrected.
SH	Royal College of Physicians London	1	NICE	General	General	The Royal College of Physicians is grateful for the opportunity to respond to the draft guideline. The guideline is overall well written and generally helpful. The guideline group is to be congratulated on the scope and assembly of the evidence base, though where evidence is unclear or lacking, the panel's narrow specialist expertise rather than syncope specialist expertise becomes apparent. We have particular concerns regarding the 'Red Flag' section. These are outlined below, along with other comments.	Thank you for your comment. We have revised the red flag section.
SH	Royal College of Physicians	2	NICE	5	15	It may be helpful to add 'whether eyes are open or closed during the event'.	We agree that this can be a useful additional observation and have added it to the list.

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	London						
SH	Royal College of Physicians London	3	NICE	5	20	There is a strong recommendation to use automated ECG interpretation, despite the Research Question suggestion that this approach has no evidence base. A rider here would be useful - stating that such automated interpretation is useful for the non-specialist, but that important conditions like short QT syndrome, bi- and tri-fascicular block, Brugada syndrome and Arrhythmogenic right ventricular dysplasia are easily missed by automated reports.	GDG discussed this, the automated ECG will pick up that ECG is abnormal, but not always correctly identify the abnormality. As it is unlikely to "miss" the abnormality, just mis-name it, the guideline recommends that all people with abnormalities are referred for specialist cardiovascular assessment, at which point the abnormalities will be checked by an expert. The GDG wished to avoid people being inappropriately discharged (false negatives). The number of abnormalities which would be completely missed by automated ECG is likely to be very small. The alternative strategy would require all ECG's to be read by an expert which is unlikely to be cost effective.
SH	Royal College of Physicians London	4	NICE	5	23	It may be useful to add: anaemia with haematocrit <30 (San Francisco Syncope Rule). The ROSE study recently published in the J Am Coll Cardiol also showed that raised BNP is helpful in risk stratification. The accompanying editorial by Benditt gives a very useful overview of why more is needed to sort out risk stratification in syncope/TLOC. It may be useful to add: supine syncope	In the full recommendations, it states that if there is another condition this should be dealt with using clinical judgment to determine urgency. it is clear We have also added a recommendation to advise clinicians to consider other conditions, if patients do not fully regain consciousness or patients may have sustained and injury.

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SH	Royal College of Physicians London	5	NICE	5	32	The term **heart murmur** is not specific enough. This requires clarification and should be amended to reflect a murmur consistent with aortic stenosis i.e. an ejection systolic murmur radiating to the carotids	Thank you for your comment. Aortic stenosis is not the only form of structural heart disease that can present with TLoC and a murmur. Hypertrophic cardiomyopathy must be considered in particular, and people with dilated cardiomyopathy or other causes of left ventricular impairment may present with TLoC due to ventricular arrhythmia and may have audible mitral regurgitation as a clue to a cardiac cause for their TLoC. These guidelines are aimed at the broad range of healthcare personnel who may encounter someone who has suffered TLoC, and not all of them will have the skills to recognise the character or even the timing of a murmur, so for these reasons we have maintained a more general description.
SH	Royal College of Physicians London	6	NICE	6	6	Consider adding 'and when 12 lead ECG is normal and there is no clinical evidence of structural cardiopulmonary disease'. Many of these features are non-specific and do not exclude a cardiac cause. However, a normal ECG and heart are extremely reassuring for the non-specialist and specialist alike.	We are required by NICE to select ten recommendations as Key Priorities for Implementation. These recommendations are taken out of context. The recommendations on ECG state that anyone with an abnormal ECG should be seen by a specialist within 24 hours. We have also added a recommendation that everyone should have an ECG within 3 days even if diagnosed with an uncomplicated faint.
SH	Royal College of Physicians	7	NICE	7	20	Consider adding 'orthostatic' Consider changing to 'suspected cardiac', and adding 'suspected steal syndrome'.	In the full list of recommendations, this has been addressed.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
	London						
SH	Royal College of Physicians London	8	NICE	7	22	There is no mention of ECHO. We believe this is needed in those with suspected structural heart disease and those with abnormal ECG.	This has been added as an example
SH	Royal College of Physicians London	9	NICE	8	11	We disagree. Tilt testing is very appropriate for older people with no warning symptoms if they have a normal heart and normal E CG. Older patients with vasovagal syncope often present atypically and should go through the same diagnostic process as the young. See review Tan and Parry, J Am Coll Cardiol 2008;51:599-606.	It has been clarified when it should not be used i.e. when I diagnosis has been confirmed and the circumstances in which it should not be used as a first line investigation.
SH	Royal College of Physicians London	10	NICE	9	20	Pressure on carotid sinus is not necessary for the definition – see McIntosh et al Am J Med 1993;95:203-8	Thank you for your comment. Most definitions of carotid sinus syncope refer to pressure on one or other carotid, whether manually during provocation testing or by tight collars, turning the head etc during normal daily activity.
SH	Royal Colleg	11	NICE	9	22	Increase in intra-abdominal pressure is by no means necessary, as in swallow syncope, blood and needle	Thank you, this has been amended.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
	e of Physicians London					phobia.	
SH	Royal College of Physicians London	12	NICE	9	29	Consider deleting 'exercise-induced syncope'. This is a symptom not a diagnosis.	Thank you for your comment. We have not suggested that exercise-induced syncope is a diagnosis. It is a useful descriptive term that describes the circumstances in which syncope has occurred and that should alert people to the possibility of a potentially high-risk underlying cause that may be a dangerous arrhythmia and/or underlying structural heart disease. When there is a clear history of exercise-induced syncope and there is no structural heart disease to explain the mechanism, an exercise test can be a very logical and useful way of either demonstrating the mechanism of syncope, or at least making an assessment of risk.
SH	Royal College of Physicians London	13	NICE	11	26	Consider adding to the list: • bradycardia <50 beats per minute – in the absence of rate limiting drugs a powerful indicator of sinus node dysfunction • LBBB and RBBB – see evidence from the ISSUE study (Brignole et al Circulation 2001;104:1261-7 • ischaemic changes around time of sycope/TLOC	Thank you for your comment. We have already included "inappropriate and persistent bradycardia" as a more generic description. This will include sinus bradycardia due to sinus node disease and bradycardia due to AV block, both of which will require consideration of pacing in someone who has suffered TLoC. We have also included the generic category "conduction abnormality". In someone who has presented withy TLoC further assessment and at least consideration of the risks and benefits of pacing will be needed if there is any degree of conduction abnormality

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
							that might predispose to intermittent more severe AV block as the cause of syncope. We have modified the wording slightly to make this clearer.
SH	Royal College of Physicians London	14	NICE	11	26	**Conduction abnormality (any degree of heart block)**. This should be made more specific. 1st degree heart block is not considered a high risk feature. It should be considered if the patient has Mobitz II 2nd or 3rd degree atrioventricular block Reference: *Task Force on syncope , European Society of Cardiology Eur Heart Journal 2001;22:1256-1306*	Thank you for your comment. Whilst a prolonged PR interval taken in isolation is not usually indicative of a high risk of more advanced AV block and sudden death, the finding of any AV conduction delay, including first degree AV block in a person who has presented with TLoC merits further assessment as it may be the only indication of an underlying conduction abnormality that caused the episode of TLoC and that requires treatment by pacing. Clearly, as you say, more advanced AV block is indicative of a high risk of recurrence and of a risk of sudden death and the indication for pacing is certain in those circumstances.
SH	Royal College of Physicians London	15	NICE	11	29	Long QT (> 450 ms) suggest different values for males and females - >450 ms in males and >460 ms in females suggesting QT prolongation. Reference: BMJ 2010;340:b4815	For simplicity the GDG agreed on the lower figure in both cases.
SH	Royal College of Physicians Londo	16	NICE	11	30	There is a need to specify the ECG abnormalities of **Brugada syndrome**. i.e. ST segment elevation in the precordial leads (V1 - V3)	Thank you for your comment. The guideline group felt that the ECG should be interpreted by someone who is competent in identifying the relevant abnormalities, so that it was not necessary to describe the specific appearance of the abnormalities in the guideline to try to teach those people how to recognise the abnormalities.

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SH	Royal College of Physicians London	17	NICE	12	3	**Left or right ventricular hypertrophy** is not associated as a high risk feature.	See previous comment. the OESIL study mentions left or right ventricular hypertrophy, so does Sun 2008 and Sarasin 2003 as part of their lists of abnormalities
SH	Royal College of Physicians London	18	NICE	12	4	Abnormal T waves is not specific enough and requires clarification. These ECG changes are a common finding. We would suggest as an alternative - Negative T waves in right precordial leads, epsilon waves and ventricular late potentials suggestive of arrhythmogenic right ventricular dysplasia	Thank you for your comment. You have focussed specifically on the T wave and other abnormalities that may be seen in ARVC (as a cause of TLoC). However other T wave inversion may be indicative of structural heart disease or ischaemic heart disease as an underlying substrate for ventricular arrhythmia causing TLoC, so we did not wish to limit the description of T wave abnormality to ARVC, which is a relatively uncommon, albeit potentially high-risk cause of TLoC.
SH	Royal College of Physicians London	19	NICE	12	6	**Atrial arrhythmia (sustained)** would result in admitting many patients with atrial fibrillation which is a common arrhythmia in the elderly.	Thank you for your comment. If an elderly person in AF experiences TLoC it seems reasonable for them to have further assessment including review of their drug therapy etc.within 24 hours. They may not require hospital admission, but that is a decision that must be based on further assessment. Some people lose consciousness due to the sudden fall in cardiac output at the onset of paroxysmal AF and others, probably more commonly, with sinus node disease and "brady tachy syndrome" have a prolonged sinyus node recovery time that results in cardiac

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							standstill for long enough to cause syncope when an episode of AF terminates spontaneously
SH	Royal College of Physicians London	20	NICE	12	16 1.1 .3. 2	Treat as an emergency (within 24 hours) anyone with TLoC who also has any of the following. This is potentially very problematic - if it means admit all these patients. We believe that this 'red flag' recommendation requires clarification otherwise it could lead to a massive increase in admissions of older people with TLOC. Many of these patients will have minor ECG abnormalities, or an innocuous murmur, or cognitive impairment which will mean that they cannot describe the prodrome. If all these patients were admitted we estimate that the service would be managing an extra 2-3 patients per day per hospital. This would provide extra pressure on acute medicine units. We understand that 'treat as emergency' does not necessarily mean admission to the hospital but this must be clarified. There are obvious and large funding implications to the recommendation otherwise and it appears to be at odds with all other current policies to avoid unnecessary hospital admission. In frail older people with TLoC, the most common cause is usually polypharmacy. This can be quickly addressed and either in primary care (+/- OPD) or in the ED or acute medicine clinics. However, these patients will likely have some of the features above, so according to the guidance will need to be admitted (unnecessarily).	Thank you for pointing this out. We have clarified the wording so that it is clear that it is an assessment within 24 hours but not necessarily admitted. We have deleted the general advice to admit. We have also added information about why a medication review should take place.

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SH	Royal College of Physicians London	21	NICE	14	21	The presence or absence of a bitten tongue is important, but it is also useful to document whether the bite was on the lateral surface of the tongue (suggestive of a convulsive seizure) or the front of the tongue (a less specific feature not uncommonly seen in syncope without convulsion). Evidence for this is lacking, but it can be useful when assessing patients after a possible first fit. If not recorded at the time in the emergency department patients can be uncertain when seen at a later date in clinic.	The GDG does not think that the position of the injury should be a factor in whether or not someone is refer. However, we agree that it would be useful to have this recorded and this has been added.
SH	Royal College of Physicians London	22	NICE	17	11	Why is the age specified at >60? ESC recommends >40. As far as we are aware there is no definitive evidence for any age cut off.	Regarding the threshold of 60 years for CSM testing, the GDG chose this limit to obtain a reasonable pre-test probability of finding CSH. A UK-based study (Humm 2006 - Unexplained syncope--is screening for carotid sinus hypersensitivity indicated in all patients aged >40 years? *J Neurol Neurosurg Psychiatry* 2006 77: 1267-1270) lent support to this cut-off point showing a very low diagnostic yield for CSM below 60 years.
SH	Royal College of Physicians London	23	NICE	19	general	Vasovagal management: There is no mention of adequate fluid intake or physical counterpressure manoeuvres vital in first line management (Blanc J Am Coll Cardiol 2006;48:1652-7)	Management post-diagnosis is beyond the scope and this section has been altered.

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SH	Royal College of Physicians London	24	NICE	General	General	The main issue here is the assumption that all syncope patients who require onward referral need to be seen by a cardiologist. Not all cardiologists have an interest in, or specific expertise in transient loss of consciousness generally and syncope specifically. They of course have expertise in cardiac causes of syncope, but as these represent less than 5% of causes in younger individuals, and around 30% of causes in older patients, referral of all who need specialist review will result in patients not being seen by experts. Geriatricians, generalists and neurologists all run and/or contribute to syncope services – in the UK. There are many syncope services run by geriatrician/general internists with cooperation and collaboration with other relevant specialties. The recent European Society for Cardiology Guidelines (Eur Heart J 2009;21:2631-71) recommend specifically that syncope services should in essence be run by those with an interest with specific recommendation as to which flavour of specialist this should be – simply specialists with the knowledge and expertise to run such a service. A related issue is that the Guideline makes no mention of the usefulness of specialist syncope/TLOC services – there is a small but decent evidence base supporting the benefits of such a service. *It is suggested that:*	The technical with GDG members have re-reviewed the evidence and reworded recommendations to make this clearer.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
						• All references to referral for "specialist cardiology assessment"(eg P6 Line 3, P7 line 9) should be changed to "specialist assessment". • Some comment should be made on the usefulness of syncope specialist services. *Syncope and TLOC* Some further discussion regarding syncope in the context of TLOC may be helpful *Definitions:* • Syncope: Most definitions of syncope include the phrase "with loss of postural tone" - this is a very helpful part of the definition both as a question for witnesses and in terms of helping clarify "where next" for the syncope first responder. • Neurally mediated syncope: There is confusion here. Neurally mediated syncope very specifically refers to vasovagal syncope, carotid sinus syndrome and situational syncope; clearly explained in the 38 page document, not so in the full document. • Orthostatic hypotension: Barely mentioned in the Guideline, though present in the full version. Autonomic failure presented as the cause, but common causes (drugs in particular) not mentioned in	

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						the appropriate place nor important rarities like Addisonism. • Throughout the Guideline has split cardiac into arrhythmic and structural causes: This may be unhelpful as the two can overlap symptomatically and pathophysiologically. Consideration should be given to using ESC Guidelines style of classification. • Exercise-induced syncope: Useful to split this – syncope during exercise – rule out sinister cause; syncope following exercise with normal ECG – generally vasovagal. *Ambulatory ECG* There is a huge emphasis on short term Holter monitoring; while the step-up approach is welcome (short term, external loop recorder, implantable loop recorder [ILR]), some idea of the limitations would be helpful here. For example, yield may be higher in those with palpitations peri-event. A negative test is unhelpful, unless there is a characteristic TLOC event with clear normal sinus rhythm reported. The other concern here is the immediate progression to ILR in very specific circumstances with no other diagnostic	

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						process involved. There is simply no evidence to support this. While the ILR can be very helpful, it should not replace a work-up that may involve much cheaper ways of getting to the same answer, *particularly* given the lack of evidence of cost-effectiveness (per research questions!).	
SH	Royal College of Physicians London	25	FULL	General	General	At 409 pages the Full Guideline is well written but could be more practical. To be of most use we would like to see it tailored to GP/emergency medicine/acute physician/cardiologist/neurologist and be of an easily digestible length. We believe that more work on identifying the key audience, implementation and consequences of the guideline is required.	The guideline follows the standard format prescribed by NICE. As is standard procedure a 'Quick Reference Guide' will be published which is more digestible. We will refer your suggestions on individualised publications to the implementation team.
SH	Royal College of Physicians London	26	FULL	General	General	There seems to be no mention of joint neurology/cardiology assessment clinics.	This is a clinical guideline giving guidance to clinicians on managing the TLoC. How to configure the service is part of implementation and may very locally in different health communities. We have been clear in the recommendations the competencies required.
SH	Royal College of Physicians	27	FULL	General	General	Recommending admission for the over 60s group is not a good use of resource. We would prefer that recommendations centre on urgent investigation with one stop clinics within a clear time scale.	We have re-worded the cardiological red flag advice, to make it clear that it need not be admission, but an assessment within 24 hours; this could be at a one-stop clinic. We have reviewed age dependent recommendations, and asked clinicians to 'consider'

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	London						referral. We have revised the recommendation on red flags so that urgent referral for all 'over 65s with no prodromes ' is something to be considered, not done unreservedly
SH	Royal College of Physicians London	28	FULL	General	General	Not everyone who blacks out needs a cardiology appointment. However, they do need a range of investigation and an opinion, which is not quite the same thing. Many GPs and physicians are able to recognise risk factors and manage them effectively e.g. knowing what to do with patients with aortic stenosis for instance.	Wording changed to define expertise
SH	Royal College of Physicians London	29	FULL	General	General	There is little made of wrong prescriptions within the guideline. Sedatives, diuretics, ACE inhibitors, alpha blockers, vasodilators all cause falls.	We have made this clearer in the recommendation about reviewing medication that this is what we were referring to.
SH	Society for Acute Medicine	1	NICE	5	32	The term heart murmur is not specific enough. Need to be stated a murmur consistent with aortic stenosis i.e. an ejection systolic murmur radiating to the carotids	Thank you for your comment. Aortic stenosis is not the only form of structural heart disease that can present with TLoC and a murmur. Hypertrophic cardiomyopathy must be considered in particular, and people with dilated cardiomyopathy or other causes of left ventricular impairment may present with TLoC due to ventricular arrhythmia and may have audible mitral regurgitation as a

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							clue to a cardiac cause for their TLoC. These guidelines are aimed at the broad range of healthcare personnel who may encounter someone who has suffered TLoC, and not all of them will have the skills to recognise the character or even the timing of a murmur, so for these reasons we have maintained a more general description.
SH	Society for Acute Medicine	2	NICE	11	26	Conduction abnormality (any degree of heart block) – This needs to be more specific. 1st degree heart block is not considered a high risk feature. It should be considered if they have Mobitz II 2nd or 3rd degree atrioventricular block Task Force on syncope , European Society of Cardiology Eur Heart Journal 2001;22:1256-1306	Thank you for your comment. Whilst a prolonged PR interval taken in isolation is not usually indicative of a high risk of more advanced AV block and sudden death, the finding of any AV conduction delay, including first degree AV block in a person who has presented with TLoC merits further assessment as it may be the only indication of an underlying conduction abnormality that caused the episode of TLoC and that requires treatment by pacing. Clearly, as you say, more advanced AV block is indicative of a high risk of recurrence and of a risk of sudden death and the indication for pacing is certain in those circumstances.
SH	Society for Acute Medicine	3	NICE	11	30	Need to specify the ECG abnormalities of Brugada syndrome i.e. ST segment elevation in the precordial leads (V1 - V3)	Thank you for your comment. The guideline group felt that the ECG should be interpreted by someone who is competent in identifying the relevant abnormalities, so that it was not necessary to describe the specific appearance of the abnormalities in the guideline to try to teach those people how to recognise the abnormalities.
SH	Society for Acute Medici	4	NICE	11	29	Long QT (> 450 ms) suggest different values for males and females - >450 ms in males and >460 ms in females suggesting QT prolongation. BMJ 2010;340:b4815	For simplicity the GDG agreed on the lower figure in both cases.

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SH	Society for Acute Medicine	5	NICE	12	3	Left or right ventricular hypertrophy is not associated as a high risk feature.	See previous comment. the OESIL study mentions left or right ventricular hypertrophy, so does Sun 2008 and Sarasin 2003 as part of their lists of abnormalities
SH	Society for Acute Medicine	6	NICE	12	4	Abnormal T waves is not specific enough and very vague. These ECG changes are a common finding. Suggest - Negative T waves in right precordial leads, epsilon waves and ventricular late potentials suggestive of arrhythmogenic right ventricular dysplasia	Thank you for your comment. You have focussed specifically on the T wave and other abnormalities that may be seen in ARVC (as a cause of TLoC). However other T wave inversion may be indicative of structural heart disease or ischaemic heart disease as an underlying substrate for ventricular arrhythmia causing TLoC, so we did not wish to limit the description of T wave abnormality to ARVC, which is a relatively uncommon, albeit potentially high-risk cause of TLoC.
SH	Society for Acute Medicine	7	NICE	12	6	Atrial arrhythmia sustained would result in admitting many patients with atrial fibrillation which a common arrhythmia in the elderly.	Thank you for your comment. If an elderly person in AF experiences TLoC it seems reasonable for them to have further assessment including review of their drug therapy etc.within 24 hours. They may not require hospital admission, but that is a decision that must be based on further assessment. Some people lose consciousness due to the sudden fall in cardiac output at the onset of paroxysmal AF and others, probably more commonly, with sinus node disease and "brady tachy syndrome" have a prolonged sinyus node recovery time that results in cardiac

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							standstill for long enough to cause syncope when an episode of AF terminates spontaneously
SH	Society for Acute Medicine	8	NICE	12	16 1.1 .3. 2	Treat as an emergency (within 24 hours) anyone with TLoC who also has any of the following. Need to specify what does this mean. Does it mean admit all these patients as this could be a problem. This could lead to a massive increase in admissions of older people with TLOC – many of whom will have minor ECG abnormalities, or an innocuous murmur, or cognitive impairment which means they cannot describe the prodrome. If we are we to admit all these people some consideration needs to given to the funding implications of managing an extra 2-3 patients per day per hospital who will get admitted – especially at a time of crisis and when all other forces are trying to avoid unnecessary hospital admission. In frail older people with TLOC, the most common cause is usually polypharmacy, which is quickly addressed and sorted either in primary care (+/- OPD) or in the ED or acute medicine clinics – but they will also have some of the features above, so according to the guidance will need to be admitted.	Thank you for pointing this out. We have clarified the wording so that it is clear that it is an assessment within 24 hours but not necessarily admitted. We have deleted the general advice to admit. We have also added information about why a medication review should take place
SH	Society of British	1	Full	General	General	This document has been reviewed by the Professional Standards Committee of the SBNS. We note that the emphasis quite correctly is on the common causes such as syncope, cardiovascular conditions and epilepsy (and	Thank you for your thoughtful consideration. We considered these rare diagnoses, and agree that they can present a diagnostic challenge. We felt that such patients are unlikely to present with (brief) loss of consciousness

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	Neurological Surgeons					related conditions). However, we are concerned and wish to highlight that TrLOC can also occur due to Acute Hydrocephalus such as in tumours of the Third Ventricle (Colloid cysts) and in patients with CSF shunts who develop blocking of the shunt. These patients may have dilated unreactive pupils and respiratory arrest or impairment during an attack. These episodes may often go undiagnosed despite repeated attacks. They reflect sudden rises of intracranial pressure and constitute a neurological emergency. It is a potentially life threatening condition and should be alerted to the Neurosurgical service as an emergency. Emergency CT or MR imaging is indicated. In suggesting amendments to the document the addition of Acute Hydrocephalus as another cause will require changes to the document in a number of places including the diagnosis (P14 –P20), P29 L4, P55 L8, P56 L14, and in the later sections pertaining to diagnostic tests and referral to specialist opinion etc. Whilst this is not a common cause of TrLOC the awareness of it is very important and the document would be incomplete without a reference to this condition	with full recovery, and without any residual neurological signs. The possibility of a serious intra-cranial disorder should therefore be apparent on careful clinical assessment; and imaging would normally be arranged as part of specialist further investigation. However we agree that it would be appropriate to alert clinicians to the possibility of acute hydrocephalus and have modified the guideline by adding a red flag recommendation about not making a full recovery.
SH	STARS - Syncope	1	Full	General	General	Members of the STARS Advisory Board have read with interest the NICE Guidelines Draft for Consultation entitled "Transient loss of consciousness (T-LOC) management in adults".	Noted with thanks

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
	Trust And Reflex anoxic Seizures					A comprehensive systematic review of the literature dealing with diagnosing T-LOC has been performed and critically appraised. This has never been done before. The NICE recommendations are based on the evidence found in the literature, but in addition also on the expertise/ experience of the members of the NICE Guideline Development Group. It is interesting to observe that the latter input seems to have been a major component of the integrated recommendations dealing with the analysis of T-LOC. It is reassuring that the recommendations are almost identical to the 2009 ESC Guidelines on Syncope, which is an expert-based document. The members of the STARS Advisory Board are appreciative of the efforts of the Nice Guideline Development Group. They have the following comments.	
SH	STARS - Syncope Trust And Reflex anoxic Seizures	2	Full	General	General	This is a monumental document but it is so long that it will be read in its entirety by only a few with a very deep interest in the subject. Perhaps because of its length the draft has a lack of focus (see 2). We suggest that this could be improved by separate sections for:- The executive summary to contain the main recommendations as care pathways The body of the guideline The analysis of the evidence-base A more detailed and modified glossary of terms	At publication there will be several versions of the guideline. As you say, the full guideline is aimed at those who have a deep interest in the guideline. This follows the standard format prescribed by NICE. The NICE guideline, is an 'executive summary' as you mention, In addition, there will be two publications printed and circulated widely. 1. the 'Quick Reference Guide' will be professionally typeset and published presenting the key information to clinicians in an accessible format. 2. The 'Understanding NICE Guidance' which will explain the recommendations to people who have neither a clinical

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							background
SH	STARS - Syncope Trust And Reflex anoxic Seizures	3	Full	1	General	Title "Transient loss of consciousness (T-LOC) management in adults". The aim of the Guideline, is "to define the appropriate pathways for the initial assessment of patients with T-LOC and so to derive the correct underlying diagnosis quickly, efficiently, and cost-efficiently, and tailor the management plan to suit their true diagnosis " (page 55). Thus the main goal of the NICE guideline seems to be in the initial differential diagnosis and triage of T-LOC. However, the document does not give equal weight to all causes of T-LOC. The emphasis of the document lies very strongly on syncope and in particular on cardiac causes, and other causes receive comparatively little attention. In fact, epilepsy, a rather important form of T-LOC, is only treated to the effect that hints are given for its recognition. Psychogenic T-LOC, another important cause of T-LOC, is hardly dealt with. Perhaps this highly focused attention is exactly what the UK needs, but in that case it would be good to adapt the title to reflect that the document does not give all forms of TLOC equal attention. A simple solution would be to change the title. The title could read something like: initial differential diagnosis and triage of T-LOC with emphasis on detection or exclusion of cardiac syncope	This guideline is closely linked with the Epilepsy guideline (CG20) and was commissioned to address some of the gaps in that guideline prior to referral to neurology. We recognise in the consultation version this link was not clear and we have made clearer the scope of the guideline in the introduction. With regard to psychogenic T-LOC, have also broadened the diagnostic pathway, adding some information and a recommendation on psychogenic pseudosyncope and PNES. The GDG has referred the topic of PNES to NICE to be developed as a guideline in its own right We acknowledge your point that some of the advice on managing the condition once a diagnosis is made is beyond the scope of the guideline and the evidence reviews and have therefore removed this to be within the scope.

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						It should also be made more clear that the systemic review and critical appraisal deals almost exclusively with diagnosing syncope, but not systematically with treatment of syncope/ T-LOC, although some treatment advices are given. This issue is dealt with shortly (a bit hidden) on page 78. When the guidelines gets into the detail of treatment at some points, they run the risk of becoming controversial. From the perspective from the STARS reviewers it might have been better to say "treatment of syncope - see ESC Guideline, treatment of Falls - see NSF for the Elderly, treatment of epilepsy - see NICE Guideline for epilepsy"	
SH	STARS - Syncope Trust And Reflex anoxic Seizures	4	Full	General	General	*Use of terminology* A major concern is the use of the terminology. For example the classification of T- LOC on page 29 and 56 in: a. Uncomplicated faint or situational syncope b. Orthostatic hypertension c. Dysfunction of the nervous system (epilepsy) d. Dysfunction of the cardiovascular system (syncope), e. Dysfunction of the psyche (psychogenic seizures)	Thank you for your comment. The classification of causes of T-LoC on page 29 is in accord with other international guidance. We accept that the original wording on page 59 is potentially confusing and have modified the text to correct this.

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						may raise confusion since category a (uncomplicated faint or situational syncope) and b (orthostatic hypotension) both fit in the concept of syncope (item d). In fact, it is not completely clear to us why NICE developed a new classification of T-LOC other than the recently updated authorative 2009 ESC guideline classification, now used worldwide. Vascular syncope and separation of suspected NMS and unexplained syncope is not useful as historically the two terms have been used interchangeably by many writers and imply the same kind of patient. Moreover even within the document different classification/terms are used, e.g. - cardiac syncope (arrhythmia based or structural heart disease based) - vascular syncope (including neurally mediated, situational, orthostatic hypotension) - epileptic seizures - psychogenic non-epileptic seizures - other causes of T-LOC - unexplained T-LOC STARS MAC believes the Glossary of Terms needs strengthening.	
SH	STARS - Synco	5	Full	General	General	Epidemiology of T-LOC The prevalence and mortality of various causes of T-LOC in England and Wales in clinical settings were determined	Not aware of a general population UK study looking at prevalence of T-LOC. In this section an attempt was made to determine the prevalence of T-LOC with available data.

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	pe Trust And Reflex anoxic Seizures					by the study group (page 29-54). No data seem to be available in the UK for T-LOC/ syncope in the general population. Knowledge about this epidemiology in the general population is from our perspective very insightful in understanding the dynamics of T-LOC in the population. This knowledge can serve as benchmark information to develop diagnostic cost effective approaches. We therefore suggest to add a paragraph to the section dealing with epidemiology saying that the frequency pattern of reflex syncope in the general population and in general practice is bimodal with a peak in teenagers/ young adults (15-40 yrs) and in the elderly (> 65 yrs). In subjects aged 40-60 yrs syncope is relatively rare. In teenagers/young adults almost all cases of transient loss of consciousness are due to reflex syncope. The life-time cumulative incidence in young females (≅ 50%) is about twice as high as in males (≅ 25%) compared to a frequency of 1% only of epileptic seizures. Cardiac syncope in this age group is extremely rare. In the elderly, cardiac causes, orthostatic- and postprandial hypotension and the effects of medications are common, whereas typical vasovagal syncope is less frequent. Reflex syncope, however, remains the most common cause of syncope in the elderly. The presentation from the general population to medical setting is very much age dependent. In the elderly about 50 % do not present to a	While the data quoted in the study cannot be disputed, it was carried out in Netherlands and one cannot assume that the figures would be the same in the UK.

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						medical setting, in the young this percentage may be as high as 90%. Reference Olde Nordkamp LRA, van Dijk N, Ganzeboom KS, Reitsma JB, Luitse JSK, Dekker LRC, Shen WK, Wieling W. Syncope prevalence in the ED compared to general practice and population: a strong selection process. Am J Emerg Med 2009;27: 271-279	
SH	STARS - Syncope Trust And Reflex anoxic Seizures	5	Full	General	General	Epidemiology of T-LOC The prevalence and mortality of various causes of T-LOC in England and Wales in clinical settings were determined by the study group (page 29-54). No data seem to be available in the UK for T-LOC/ syncope in the general population. Knowledge about this epidemiology in the general population is from our perspective very insightful in understanding the dynamics of T-LOC in the population. This knowledge can serve as benchmark information to develop diagnostic cost effective approaches. We therefore suggest to add a paragraph to the section dealing with epidemiology saying that the frequency pattern of reflex syncope in the general population and in general practice is bimodal with a peak in teenagers/ young adults (15-40 yrs) and in the elderly (> 65 yrs). In subjects aged 40-60 yrs syncope is relatively rare. In teenagers/young adults almost all cases of transient loss of consciousness are due to reflex syncope. The life-time cumulative incidence in young females (≅ 50%) is about	Not aware of a general population UK study looking at prevalence of T-LOC. In this section an attempt was made to determine the prevalence of T-LOC with available data. While the data quoted in the study cannot be disputed, it was carried out in Netherlands and one cannot assume that the figures would be the same in the UK.

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						twice as high as in males (≅ 25%) compared to a frequency of 1% only of epileptic seizures. Cardiac syncope in this age group is extremely rare. In the elderly, cardiac causes, orthostatic- and postprandial hypotension and the effects of medications are common, whereas typical vasovagal syncope is less frequent. Reflex syncope, however, remains the most common cause of syncope in the elderly. The presentation from the general population to medical setting is very much age dependent. In the elderly about 50 % do not present to a medical setting, in the young this percentage may be as high as 90%. Reference Olde Nordkamp LRA, van Dijk N, Ganzeboom KS, Reitsma JB, Luitse JSK, Dekker LRC, Shen WK, Wieling W. Syncope prevalence in the ED compared to general practice and population: a strong selection process. Am J Emerg Med 2009;27: 271-279	
SH	STARS - Syncope Trust And Reflex anoxic	6	Full	General	General	*Convulsive syncope* The Guideline's main focus in dealing with vasovagal syncope is the simple/ uncomplicated faint. It is mentioned that "myoclonic jerks" may occur, but it could be considered to emphasize that a vasovagal syncope with impressive jerks does not look like or sound like a simple faint at all. There is often abrupt loss of consciousness, there may be injuries, there may be impressive shaking or	Thank you for your comment. As you say, the guideline already emphasised that brief seizure activity may occur during syncope. We have modified the text further to emphasise the difference between descriptive terms (such as convulsive syncope) and mechanistic terms (such as vasovagal syncope). Convulsive syncope may be observed during some forms of cardiac syncope and is not confined to a vasovagal (reflex) mechanism. The guideline aims to

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	Seizures					jerking of the limbs, there may be incontinence, the loss of consciousness may be quite prolonged, and the patient may be drowsy or feel ill afterwards. These patients easily get labelled with epilepsy and sent immediately to a neurologist. Once there, they often get stuck with a diagnosis of epilepsy and with epilepsy drugs. We know that this happens all too frequently. Indeed, the 2007 All-Party Parliamentary Working Group on Epilepsy in England reported that there were at least 74,000 patients with a misdiagnosis of epilepsy in England alone, and these were patients taking epilepsy drugs. There might be many more with a label of epilepsy hanging over them. We would like to see "convulsive syncope" added to the list of syncopes.	direct only those with strong features suggesting epilepsy towards neurological assessment, for the reasons that you have highlighted
SH	STARS - Syncope Trust And Reflex anoxic Seizures	7	Full	General	General	*Tilt table testing.* Tilt testing is addressed aggressively and dismissively. It has to be remembered that many referrers for this test are not at all well versed in the investigation of syncope. Furthermore, tilt testing as well as some of the time diagnosing NMS it diagnoses Orthostatic Hypotension, Psychogenic Pseudosyncope and POTS. As written the present document will force tilt testing into the background to the detriment of overall diagnoses in this field. Today, tilt testing must include a drug challenge and the evidence is in favour of GTN being superior to Isoproterenol. Much is written about the sensitivity and specificity of tilt testing when there is no gold standard. Furthermore, the largest series of tilted normals of all ages (Petersen et al, Heart 2000) is not quoted. This study	Thank you for your comments. The guideline development group recognised that there is a tendency for tilt testing to be requested inappropriately by those without a clear understanding of the uses and limitations of tilt testing. For the investigation of unexplained syncope, the evidence reviewed favoured the initial use of event recorders (external or implanted) rather than tilt testing. It is hoped that most cases of orthostatic hypotension would be diagnosed by careful history and clinical assessment and that diagnosis using formal tilt testing to detect fleeting "initial" OH or to detect delayed, progressive falls in blood pressure on standing would be needed in a minority in whom there was no clue from the history or from clinical measurements of blood pressure after standing.

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						indicated a false positive rate of approximately 13%, although admittedly this was for passive tilt, and there are reports that the false-positive rate for tilt-testing may be as high as 50% when isoproterenol is used in addition to passive tilt alone. Reproduction of syncope on tilt cannot be considered a pleasant experience but it is equally unpleasant if it recurs spontaneously. It is wrong to claim that there is a risk with tilt testing and use of a drug challenge, especially GTN, does not increase the hazard for the patient. There is no need for a tilt table test when the diagnosis of vasovagal syncope is well supported clinically, but tilt table testing can certainly help to elucidate the mechanism of T-LOC when symptoms are reproduced. Often additional aspects of the medical history missed during the initial interview come up. In addition a tilt table test is important for explication of symptoms and teaching physical counterpressure manoeuvres. Tilt table testing, when accompanied by beat to beat BP, continuous HR, ECG, respiratory monitoring, video, EEG monitoring, is a very specialistic investigation. Whilst tilt-testing should no longer be used as the standard test for diagnosis in suspected syncope, there are some aspects of tilt table testing that are not covered by an analysis of the test performance of this procedure.	The use of tilt testing to assess autonomic function in other conditions such as POTS is outside the scope of this guideline. Although tilt testing can help to make the diagnosis of pseudosyncope, when people with unexplained syncope undergo tilt testing the number of unselected people with unexplained TLoC who prove to have pseudosyncope is very low (e.g. 0.3%). The guideline recommends use of external or implantable event recorders as the first-line investigation, with appropriate assessment and consideration of other causes of TLoC if this shows that there is no abnormality of heart rate or rhythm causing a recurrent episode. The guideline does not address the Petersen 2000 study because one of the inclusion criteria for the guideline is that at least some of the patients must have had TLoC,
SH	STARS - Synco	8	Full	General	General	*Carotid sinus massage.* Carotid Sinus Syndrome is Carotid Sinus Massage with reproduction of symptoms and spontaneous syncope. This	What you say is correct, however this is a guideline not a medical textbook and the health professionals will have training on this.

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	pe Trust And Reflex anoxic Seizures					point is not made clear. Today, this is only safely done on the tilt table so as to be able to perform upright massage. No attention is given to Vasodepressor Carotid Sinus Syndrome. CSS is better as Syndrome than Syncope. The mortality of CSS is considered to be in its co-morbidity not in the recurrence of syncope (see below in terms of QALYS.) A crucial aspect of CSM is whether the investigator requires reproduction of symptoms. If so the asystolic period usually is much longer than 3.5 s (6-7 s). As far as pacing in patients with cardio-inhibitory carotid sinus hypersensitivity a Cochrane Systemic Review is on its way. Its conclusions will be quite different from the NICE draft. This is another example where going into details about treatment weakens the document.	The Cochrane review protocol aims to investigate the effectiveness of pacemakers in a combined population of spontaneous CSH and induced CSS. The purpose of our pacemaker review was to inform the diagnostic review of CSM in identifying people who would benefit froma pacemaker.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	9	Full	General	General	*Gold standard.* A main methodological problem with critical appraisal of diagnostic tests used to evaluate T-LOC is that the "gold standard" to assess an index test is not available. The NICE investigators use "expert clinicians" as their reference standard, but this index for obvious reasons will not be of identical quality among different studies. The only "semi gold standard" to evaluate studies focussing on diagnosing T-LOC is the combination of expert opinion and long-term follow up. This crucial issue could be addressed.	The reference standard in the protocols for the initial stage diagnostic reviews is indeed "Diagnosis by expert clinician (following second stage tests); and follow up." (page 88). However, some of the studies reported the reference standard of expert clinician (diagnosis following secondary tests). We have commented on page 150 that the reference standard of expert clinician is not a true reference standard. In chapter 5 we state the reference standard is ECG anomalies for the ambulatory ECG review and expert clinician for the other reviews: we do not believe follow up would be appropriate for these second stage tests. Finally in chapter 6 we used the reference standard

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							"Symptom free after pacing" (i.e. follow up), but acknowledge and discuss the limitations of this reference standard (page 350)
SH	STARS - Syncope Trust And Reflex anoxic Seizures	10	Full	General	General	Psychogenic syncope. Psychogenic causes of T-LOC are not uncommon. The ESC guidelines refers to this condition as psychogenic pseudosyncope. In the neurological literature comparable episodes, i.e., with pronounced movements, are labeled as Psychogenic Nonepileptic Seizures (PNES). Only the latter condition is addressed in the NICE draft. Psychogenic pseudosyncope is hardly mentioned. Five to ten percent of all comers in the setting of syncope units come with Psychogenic Pseudosyncope, but in this setting almost no patients with PNES are encountered. This is a major weakness. The guidelines communicate implicitly that these conditions are a diagnosis of exclusion. By doing so positive pointers in the history are de-emphasized, such as very frequent unexplained episodes, mainly young females and a typical presentation. Moreover, observation of spontaneous episodes in video recordings is not discussed, and neither are provocation tests such as tilt table testing, which is very useful to obtain a certain diagnosis. In fact, there is a considerable body of literature on factual features, which suggest that a diagnosis of a psychogenic cause is likely. Admittedly, most of this literature contrasts PNES with epileptic seizures and does	Thank you for your helpful comments and we agree with your view. Developing a guideline in the requisite time requires a prioritisation of the scope. We have broadened the diagnostic pathway, adding some information on psychogenic pseudosyncope and PNES. However, we did not have the capacity to fully review the evidence base for this topic – and one small review is included. This relates to diagnostic test accuracy of signs and symptoms for psychogenic pseudosyncope. The view of the GDG is that this subject merits its own guideline and has referred the topic to NICE. We have, however, added a recommendation that health care professionals should consider psychogenic pseudosyncope and PNES if a person has persistent unexplained TLoC.

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						not compare PNES with syncope. Nevertheless this literature should be considered here because facts which may help to make a diagnosis of PNES later should be recorded when patients with TLOC first meet a health professional, and should be communicated when patients are referred to a specialist.	
SH	STARS - Syncope Trust And Reflex anoxic Seizures	11	Full	General	General	Drugs. When drugs are discussed in relation to syncope it is important not to omit the recent onset of diuretics being very provocative of NMS in older patients who often have a history of NMS as a young person although this can be difficult to obtain.	This has been added under initial assessment. We did not find any evidence in the literature for medication in relation to a differential diagnosis of NM syncope.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	12	Full	General	General	*Brugada syndrome.* Studies attempting to diagnose Brugada syndrome on a single 12 lead ECG should not be taken seriously as any patient who has a FH of SCD at an age under 40 and shows a normal or near normal ECG deserves further study with an Ajmaline test.	Thank you for your comment. The first priority in the guideline in relation to ion channel disorders is to make sure that people with TLoC have an ECG recorded and examined for relevant abnormalities as part of their initial assessment. The GDG recognises that provocation testing with flecainide or ajmalin is indicated in the circumstances that you have described and this is in no way precluded or discouraged by the guideline

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SH	STARS - Syncope Trust And Reflex anoxic Seizures	13	Full	General	General	Epilepsy The guidelines do not discuss the use (and abuse) of EEG in the investigation of patients with T-LOC. Many clinicians are still tempted to use EEG as an investigation for all cases of T-LOC, although this test is associated with a high risk of false positive interpretations. The same can be said about the use and abuse of imaging (MRI, CT) in the context of T-LOC. There are several reasonably large studies which describe the yield of EEG and MRI in the TLOC setting (for instance the studies by Kotsopoulos and the somewhat dated Australian study by King et al.). The document despite being about T-LOC does not engage very deeply with the diagnosis of epilepsy. The focus seems to be on the differential diagnosis of syncope. Two points, which could be raised in this context, are the delay in the onset of abnormal movements that occurs in NMS and does not occur in epilepsy. Secondly, there is no discussion of the part of the tongue that is bitten in epilepsy versus that which occasionally occurs in NMS. Why use the term bedwetting when incontinence of urine is implied. If this really means that the attack has taken place during the night when asleep then the diagnosis is much more likely to be epilepsy.	Thank you for this comment. We have now added a specific reference to the use of EEG. With regard to epilepsy, This guideline is closely linked with the Epilepsy guideline (CG20). It was never intended from a commissioner perspective to fill gaps in that guideline. Thekey aim for this guideline was to provide signposting for people experiencing TLoC to the right patient referral routes . We recognise in the consultation version this may not have been clear. With regard to the differential diagnosis of epilepsy, the GDG notes the comment about the site of tongue bite, we are aware of this clinical pointer but the evidence we reviewed had much uncertainty around the estimate of the likelihood ratio so we did not feel confident in recommending the specific site rather than general tongue biting, for which there was fairly strong evidence. Likewise, although we agree with the observation that there may be a delay before the onset of abnormal movements in "convulsive syncope" we did not find this in published evidence. Regarding 'bedwetting' - we have reported the signs and symptoms exactly as described in the study. A second study (now included) investigated 'urinary incontinence' as

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							a predictor for epileptic seizures compared with syncope and found no significant difference. This heterogeneity between studies could be caused by differences in study quality or could be differences in terminology - we assume the term 'bedwetting' is more specific (meaning urinary incontinence at night). In view of this uncertainty, we did not include either term as a predictor for epilepsy.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	14	Full	General	General	Qualys. NICE is obsessed with QALYS. While these are very important in assessing treatment of mortal diseases they have no relevance in assessing non-mortal conditions. It must be remembered that the vast majority of patients we see with T-LOC have a non-mortal explanation of their problem. In the light of this fact the committee seems to fail to understand that quite a number of patients who show SND and AVB on ambulatory monitoring are actually showing this because they have had a NMS. So mortality figures cannot be translated from those with intrinsic conduction tissue disease to this group of patients. What really matters here is recurrence for two main reasons: recurrence is very disabling and depressing for the patient and recurrence becomes very expensive when it is repeatedly dealt with by ambulances, A & E and many irrelevant tests such as Brain scans and EEGs.	The use of Quality adjusted life-years (QALYs) as an overall measure of health outcome is consistent with NICE's reference case for economic evaluations. QALYs incorporate both survival gains and improvements in health related quality of life (HRQoL). The economic models developed to inform the guideline incorporate an estimate of the HRQoL improvement that results from treatments which prevent recurrence regardless of whether there is any survival gain. The reduction in resource use that results from treatments which prevent recurrence has also been incorporated in the models. The economic models also incorporate estimates of survival gains where this was considered to be appropriate by the GDG. We accept that the survival gains associated with treating patients with transient AV block during syncope may be lower than the survival gains reported in the Devon Heart Block and Bradycardia Survey (Shaw 1985). We have therefore conducted an additional sensitivity analysis in which we

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							assume no survival gain from treating AV block. Whilst this increased the ICERs, the increase was not sufficient to alter the GDG's conclusions that ambulatory ECG is likely to be cost-effective for people with suspected arrhythmia or unexplained TLoC after the initial assessment.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	15	Full	General	General	ILRs. The latest technology of ILRs. is not taken into account. Newer devices have much larger memories and longer lifetimes which limit the loss of data on T-LOC with nothing recorded. This seems to puzzle the committee. Furthermore, use of remote data transfer via the internet almost eliminates this problem because data are downloaded daily and the memory never becomes overloaded. There does not seem to be a full understanding of what is implied by T-LOC with no arrhythmia. This phenomenon has as its explanation vasodepressor NMS, PPS and possible PNES although recording of artefact would be expected in this condition. The Australian MSAC assessment of cost-effectiveness of ILRs is too out of date to be used as it can only apply to the first generation of these devices. To compare old studies of Holters with newer studies of ILRs can only be confusing and misleading.	Thank you for your comment. The GDG have considered the evidence that is currently available. Whilst this may relate to older devices it is not possible to know whether newer devices are more clinically useful until studies reporting the use of these newer devices are published. Transient loss of consciousness (TLoC) without arrhythmia was included as an outcome in both the diagnostic reviews and the economic model as the GDG considered this to be helpful in diagnosing non-arrhythmic causes. The Australian MSAC assessment was reviewed and presented to the GDG, but was considered to have potentially serious limitations and was not directly applicable to the UK. For this reason a new economic evaluation was conducted to assess the cost-effectiveness of ambulatory ECG in people who have had TLoC.
SH	STARS - Syncope Trust	16	Full	General	General	*Update references.* It would be helpful to be informed about the final date of the Systematic Searches. Some studies directly relevant for the Guideline appeared late in 2009 after publication of the 2009 ESC Syncope Guideline.	The last date for update searches was November 2009 (see page 212). The paper cited was published in December 2009. However, we have chosen to update the reviews in chapter 3 on the basis of this reference and others because it is of better quality than the included

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	And Reflex anoxic Seizures					*Reference*: Romme JJCM, van Dijk N, Boer KR, Bossuyt PPM, Wieling W, Reitsma JB. Diagnosing vasovagal syncope based on quantitative history-taking: validation of the Calgary Syncope Symptom Score. Europ Heart J 2009;30:2888-2896	studies, and leads to a change in the recommendation for vasovagal syncope. Significant reworking has been undertaken in order to provide greater clarity within an extremely difficult evidence base.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	17	Full	9	General	Comment. We would like to suggest to start by establishing that TLOC was indeed present. Based on history taking there should be evidence of abnormal reactivity, of abnormal motor control and of amnesia for that period (see Van Dijk et al Nature Reviews Neurology 2009; for suggestions) *Comment.* Incontinence (more common in epilepsy than in non-epileptic seizures!) should be mentioned	We agree that establishing that loss of consciousness has occurred can be difficult particularly if the event was unwitnessed; we note for instance that many elderly people who fall are amnesic for the actual fall. Nevertheless we can only take patients as they present, and have produced guidelines assuming that it has been established that loss of consciousness occurred, We agree that this is dependent on a witness and emphasize the importance of this. With regard to incontinence, the guideline aims to direct only those with strong features of a differential diagnosis of epilepsy compared to syncope towards neurological assessment. In this respect, the literature found heterogeneity between studies (one reporting 'bedwetting' – significant – and the other 'urinary incontinence' – not significant).
SH	STARS - Syncope Trust	18	Full	10	5	*Comment.* Add unusual triggers like diving, alarm clock going off	The GDG felt that it was inappropriate to try and provide an exhaustive list of all possible triggers, as in practice these should be apparent if a careful history is taken.

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SH	STARS - Syncope Trust And Reflex anoxic Seizures	19	Full	10	9	Comment: we would suggest to drop 'uncomplicated faint'. Alternatively, the terms "simple faint", "complex faint" or "convulsive syncope" should be included and defined in more detail to remove confusion	The patient representatives were against the use of the term simple faint as being dismissive of the event. Recognising that one of the main aims of this guideline is that patients will be referred appropriately and promptly, the other terms may only confuse and delay referral. Based on this comments and others, we have clarify the terminology
SH	STARS - Syncope Trust And Reflex anoxic Seizures	20	Full	10	12	*Comment. '*Seizure activity' can cause much confusion, which can be prevented to using 'jerking movements or another literal description instead, or providing a detailed definition in the glossary.	The GDG felt that it was important to retain the term "seizure activity" as it highlights the potential diagnostic difficulty, but agreed that the description could be expanded to include "jerking movements resembling those seen in epilepsy.

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SH	STARS - Syncope Trust And Reflex anoxic Seizures	21	Full	10	19	*Comment.* Add nausea as prodromal symptom. Sweating, pallor and nausea can occur before as well as after the faint. The text now suggests that sweating occur before LOC and nausea afterwards.	Following our revision of the vasovagal syncope review in the light of a new study published after the submission of the draft guideline, we have determined that post-TLoC nausea is not a strong independent predictor of vasovagal syncope specifically and there is uncertainty around this predictor. We have therefore removed it from the recommendation. The evidence showed that most prodromal symptoms and pallor, either pre- or post-TLoC were weak predictors, but significantly in favour of vasovagal syncope. The multivariable analysis was specific to sweating or a warm feeling pre-TLoC, but the GDG extended the item to include other prodromal symptoms pre-TLoC in order to help clinicians conducting assessment.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	22	Full	10	15	We don't know where the 6 P's come from but one of the most significant pointers to a diagnosis of syncope (in several studies) is the absence of post-event amnesia or disorientation.	We have revised the review on vasovagal syncope in the light of new studies published following the submission of the draft guideline. This together, with a closer inspection of evidence quality (including precision of the estimates) led to a revised recommendation including only the symptoms that the GDG were confident predicted vasovagal syncope. The recommendation for vasovagal syncope is a differential diagnosis for VVS compared with all other forms of TLoC. It is therefore in two sequential parts – exclusion

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							of predictors in favour of all other types of TLoC, and then specific indicators for vasovagal syncope (usually in comparison with other forms of syncope). Post-event amnesia and disorientation are predictors for epileptic seizures and have been included in that recommendation. The recommendation for vasovagal syncope states that 'there are no features that predict an alternative diagnosis', so a lack of post-event amnesia or disorientation is covered.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	23	Full	11	3	*Comment.* Once more there is 'seizure activity'. Substituting a literal description is clear and cannot confuse anyone.	The GDG felt that it was important to retain the term "seizure activity" as it highlights the potential diagnostic difficulty, but agreed that the description could be expanded to include "jerking movements resembling those seen in epilepsy.
SH	STARS - Syncope Trust And	24	Full	11	6	*Comment*. head turning during T-LOC has also been described in patients with spontaneous and laboratory provoked syncope Poles C, Boycott M. Syncope in blood donors. Lancet 1942 : 531-535	We note these references, however more recent evidence suggested that head turning is a useful discriminator, pointing to a diagnosis of epilepsy.

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	Reflex anoxic Seizures					Gastaut H, Fischer-Williams M. Electro-encephalographic study of syncope: its difference from epilepsy. Lancet 1957:2:1018-1025	
SH	STARS - Syncope Trust And Reflex anoxic Seizures	25	Full	11	25	"the category "unexplained" should be changed to "cardiologically unexplained")	We feel this is clear and it is generally unexplained.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	26	Full	11	10	*Comment*. Those who already know which symptoms and signs constitute 'presyncope' will not be confused by this statement, but those who do not, might well interpret the various 'aura sensations of an epileptic seizure as 'presyncope'. A literal description might be better.	We agree that "pre-syncope" needs clearer definition and have altered the statement.
SH	STARS	2	Full	11	14	Comment. While not intended, some people might read	Thank you for your comment. The reason for this emphasis

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	- Syncope Trust And Reflex anoxic Seizures	7				only this introduction and conclude that every patent should receive 'specialist cardiology assessment and diagnosis'. This is particularly important as there is no similar section for epileptic seizures.	is that the reader is looking at the key recommendations section, which is restricted to a maximum of 10. There is a corresponding section for epileptic seizures in the full set of recommendations (page 18).
SH	STARS - Syncope Trust And Reflex anoxic Seizures	28	Full	12	General	*Comment.* Evaluation of the orthostatic blood pressure response is part of the Initial evaluation, but the assessment is hardly addressed. See comment page 18 line 5-15.	Thank you for your helpful comments. The GDG recognises that a full review of the literature on orthostatic hypotension (including in patients without TLoC) is needed to identify correct definitions for orthostatic hypotension and to consider alternative tests such as tilt testing. We therefore changed the recommendation to describe the orthodox method, but also to say that the person should be referred for further cardiovascular assessment if the person has a suggestive history of OHT that is not confirmed by the simple test. We also revised recommendation to indicate that not every person with TLoC should have a supine/standing blood pressure test.
SH	STARS - Syncope	29	Full	13	11	"vasovagal syncope is mediated by excessive or inappropriate vagal activity" Comment.The driving mechanism inducing the fall in blood pressure in an orthostatic vasovagal syncope is a	The study quoted is the first to contradict the conventional thinking about the pathophysiology of vasovagal syncope. Done in a small group (n=56) of patients. It results would need validating in other studies. Please see comments by

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	Trust And Reflex anoxic Seizures					decrease in cardiac output. Fainting occurs with a fall of 40-50%. The vagally induced bradycardia. The other mechanism underlying vasovagal syncope is a decrease in vasomotor tone. Verheyden Bart, Liu Jiexin, van Dijk Nynke, Westerhof Berend E., Reybrouck Tony, Aubert André E., Wieling Wouter: Steep fall in cardiac output is main determinant of hypotension during drug-free and nitroglycerine-induced orthostatic vasovagal syncope.Heart Rhythm 2008;5:1695-1701	Satish R Raj on this article: 'While provocative, these findings require replication (ideally with sympathetic nerve recordings) to put them in proper physiological context'.Heart Rhythm 2008;5 (12):1702-1703
SH	STARS - Syncope Trust And Reflex anoxic Seizures	29	Full	13	11	"vasovagal syncope is mediated by excessive or inappropriate vagal activity" Comment.The driving mechanism inducing the fall in blood pressure in an orthostatic vasovagal syncope is a decrease in cardiac output. Fainting occurs with a fall of 40-50%. The vagally induced bradycardia. The other mechanism underlying vasovagal syncope is a decrease in vasomotor tone. Verheyden Bart, Liu Jiexin, van Dijk Nynke, Westerhof Berend E., Reybrouck Tony, Aubert André E., Wieling Wouter: Steep fall in cardiac output is main determinant of hypotension during drug-free and nitroglycerine-induced orthostatic vasovagal syncope.Heart Rhythm 2008;5:1695-1701	The study quoted is the first to contradict the conventional thinking about the pathophysiology of vasovagal syncope. Done in a small group (n=56) of patients. It results would need validating in other studies. Please see comments by Satish R Raj on this article: 'While provocative, these findings require replication (ideally with sympathetic nerve recordings) to put them in proper physiological context'.Heart Rhythm 2008;5 (12):1702-1703
SH	STARS - Synco	30	Full	13	17	Carotid Sinus Syncope. "on one or other artery causes syncope *Comment:* on one or other artery causes bradycardia and	Thank you for your comment. The definition states that this is a form of neurally mediated (reflex) syncope, so the occurrence of bradycardia and/or hypotension is implicit in

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	pe Trust And Reflex anoxic Seizures					vasodilatation resulting in hypotension and syncope. True symptomatic carotid sinus syncope in which iatrogenic external pressure on the neck causes faints is exceedingly rare. Miction syncope is probably much more common, but is not mentioned. Possibly a need was felt to incorporate 'carotid sinus hypersensitivity', but the two are not the same	that definition. *Micturition* syncope is included in the guideline as one of the forms of "situational" syncope. The term "miction syncope" is not used commonly in the UK, but is used more in other parts of Europe and in the US. The guideline group was careful to differentiate between CS syncope and CS hypersensitivity. The guideline relates to people who have experienced TLoC and as such the focus is on establishing the cause from the history and subsequent assessment. If the history is suggestive of or consistent with CSS and there is no evidence of another cause and carotid sinus massage reproduces syncope there is a strong likelihood that CSS was the cause of TLoC.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	31	Full	13	19	Situational syncope. "usually involving an increase in intra-abdominal pressure (for example, cough syncope and micturition syncope) *Comment:* Situational syncopes (swallowing syncope, cough syncope, micturition/ defecation syncope) are defined by "situations", but the underlying mechanisms are very different. An increase in abdominal pressure is certainly not considered a common underlying mechanism by physiologists. Cough syncope is caused by reflex vasodilatation induced by the very high arterial pressure transient induced by coughing. In micturition syncope there is a central role for a decrease is vasomotor tone induced by emptying the bladder. It could also be mentioned that many other reflex syncopes	Thank you for your comment. The text has been modified appropriately in the light of your helpful observations.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
						conventionally not included in "Situational syncopes" have a typical situational component that is crucial in diagnosing them. Examples are post-exercise hypotension, postprandial hypotension, bloodphobia etc.	
SH	STARS - Syncope Trust And Reflex anoxic Seizures	32	Full	14	3	Comment. Incontinence (more common in epilepsy than in non-epileptic seizures!) should be mentioned.	The guideline aims to direct only those with strong features of a differential diagnosis of epilepsy compared to syncope towards neurological assessment. In this respect, the literature found heterogeneity between studies (one reporting 'bedwetting' – significant – and the other 'urinary incontinence' – not significant). This heterogeneity could be caused by differences in study quality or could be differences in terminology. In view of this uncertainty, we did not include either term as a predictor for epilepsy relative to syncope, The GDG was not confident in the limited evidence reviewed for psychogenic pseudosyncope to differentiate at the initial stage between psychogenic syncope/PNES and epilepsy or syncope. Therefore, it was preferred to investigate psychogenic TLoC after other tests had been carried out. We have added a recommendation that health care professionals should consider psychogenic pseudosyncope and PNES if a person has persistent unexplained TLoC, and noted that differentiation between PNES and epileptic seizures is complex requiring specialist

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
							neurological assessment..
SH	STARS - Syncope Trust And Reflex anoxic Seizures	33	Full	16	3	Comment. insert "corrected QT" in front of 450ms and 350ms	Thank you, this has been changed
SH	STARS - Syncope Trust And Reflex anoxic Seizures	34	Full	16	30	Comment. Add unusual triggers like diving, alarm going off.	The GDG felt that it was inappropriate to try and provide an exhaustive list of all possible triggers, as in practice these should be apparent if a careful history is taken.
SH	STARS - Syncope	35	Full	17	11	Comment. 'Seizure activity' is potentially misleading. We would like to suggest "repetitive myoclonic jerking"	The GDG felt that it was important to retain the term "seizure activity" as it highlights the potential diagnostic difficulty, but agreed that the description could be expanded to include "jerking movements resembling those

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
	Trust And Reflex anoxic Seizures						seen in epilepsy.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	36	Full	17	21	*Comment.* Add nausea as prodromal symptom.	The evidence for nausea as a prodromal symptom was not as strong as for sweating and feeling hot so we left the latter two as examples.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	37	Full	17	26	*Comment.* Absence of post-event amnesia or disorientation!	The GDG did not want this list to be too complex, post-event abnormal behaviour is referred to in the epilepsy recommendation.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
SH	STARS - Syncope Trust And Reflex anoxic Seizures	38	Full	18	5-15	*Comment.* Orthostatic hypotension is an important cause of T-LOC in the elderly. An fall in systolic blood pressure > 20 mm Hg is given as a criterium. This value goes back to a Consensus Statement meeting of the American Autonomic Society from 1996. However, both older and more recent data document that this 20 mmHg only applies to subjects with a normal supine blood pressure. In addition initial orthostatic hypotension and delayed orthostatic hypotension are now recognised as special conditions. Initial orthostatic hypotension is at least as frequent as other "situational syncopes". These issues are addressed in a recent Editorial in J Hypertension and a Revion of the American Autonomic Society Consensus statement incorporating these new ideas is on its way. - Wieling W, Schatz IJ. The consensus statement on the efinition of orthostic hypotension: a revisit after 13 years. J Hypertension 2009;27:935-938 - Federowski A, Bum P, Melander O. Orthostatic hypotension in genetically related hypertensive and normotensive subjects. J Hypertension 2009;27:976-982 There is a risk of confusing 'orthostatic hypotension' with 'syncope due to orthostatic hypotension'. The definition relates to OH, a measurement result, while statements such as 'no features suggesting an alternative diagnosis' seem to point to signs or symptoms caused by OH. This problem recurs later on (section 3.5.3). Please do not	Thank you for your helpful comments. The GDG recognises that a full review of the literature on orthostatic hypotension (including in patients without TLoC) is needed to identify correct definitions for orthostatic hypotension and to consider alternative tests such as tilt testing. We therefore changed the recommendation to describe the orthodox method, but also to say that the person should be referred for further cardiovascular assessment if the person has a suggestive history of OHT that is not confirmed by the simple test. We also revised recommendation to indicate that not every person with TLoC should have a supine/standing blood pressure test. The definition of orthostatic hypotension used in the consultation version of the guideline was taken from the study reviewed (van Dijk 2008) which examined the diagnostic test accuracy of the ESC guidelines. This included in its definition "a decrease of systolic blood pressure to < 90 mm Hg", which the ESC guidelines update of 2004 referred back to the 1996 consensus statement. [We note that the 2009 update of the ESC guidelines no longer uses this definition]. What the review should have done was to identify this definition (the index test) as indirect in terms of the widely accepted definition. This has been corrected in the text and removed from the recommendation.

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						equate OH with 'syncope due to OH'. In quite a few people with severe autonomic failure you hardly encounter syncope while OH causes serious daily problems! Finally, a single erect blood pressure is inadequate to diagnose OH.	
SH	STARS - Syncope Trust And Reflex anoxic Seizures	39	Full	19	12	"all other people". *Comment.* This will include cases of psychogenic TLOC, which cannot be what you want.	The guideline aims to direct only those with strong features of a differential diagnosis of epilepsy compared to syncope towards neurological assessment. The GDG was not confident in the limited evidence reviewed for psychogenic pseudosyncope to differentiate at the initial stage between psychogenic syncope/PNES and epilepsy or syncope. Therefore, it was preferred to investigate psychogenic TLoC after other tests had been carried out, which implies that people with psychogenic TLoC are indeed referred for further assessment. The referral recommendation has been revised to say 'assessment by a specialist blackout or syncope service if available, or otherwise for assessment in a cardiology service' We have added a recommendation that health care professionals should consider psychogenic pseudosyncope and PNES if a person has persistent unexplained TLoC.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
SH	STARS - Syncope Trust And Reflex anoxic Seizures	40	Full	21	16-20	- Consider a tilt test to assess whether the syncope is accompanied by a severe cardioinhibitory response (usually asystole) *Comment.* The emphasis on cardio-inhibition is unclear. Severe cardio-inhibition in young subjects has an excellent prognosis and does not need specific treatment. Pacing is not indicated. In the elderly the data suggest that a long asystole predicts asystole in real life and pacing could be considered. The ISSUE 3 study is aimed to document that pacing is evidence based effective.	This is beyond the scope of the guideline as it is about treatment. Thank you for your comment. Some people with severe, prolonged cardioinhibition during vasovagal syncope suffer injury (including hypoxic brain injury if they are kept upright) or a reduced quality of life, especially if the episodes are frequent. In those people pacing may provide symptomatic benefit and some protection against injury, even though the risk to their life is very low. As you say, as people get older the potential benefit from pacing in this setting increases and there is likely to be some prognostic benefit. Additional evidence from the ISSUE 3 study is awaited with interest.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	41	Full	21	21-31	The criteria for CSH are not given. The > 3 s pause is a very problematic criterium, since it increases markedly with age. In healthy subjects > 80 yrs it may be as prevalent as 40% in the population.	Thank you for your comment. The guideline development group did not include details of the diagnostic criteria for carotid sinus hypersensitivity since this may be present in the absence of carotid sinus syncope. The guideline focuses specifically on those whose history is suggestive of or consistent with CSS and in whom carotid sinus massage reproduces syncope due to a bradycardic and/or hypotensive response
SH	STARS - Syncop	42	Full	21	26	A bitten tongue *Comment*: add lateral	Thank you for your comment. The classification of causes of T-LoC on page 29 is in accord with other international guidance. We accept that the original wording on page 59

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	e Trust And Reflex anoxic Seizures						is potentially confusing and have modified the text to correct this.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	43	Full	24	5	(such as contracting calf or arm muscles or buttocks if they are standing for long periods). *Comment*: this is another example where it becomes very clear that the available literature has not been searched systematically as far as recommendations about treatment are concerned. - Krediet CTP, van Dijk N, Linzer M, van Lieshout JJ, Wieling W. Management of Vasovagal Syncope: Controlling or Aborting Faints by Leg Crossing and Muscle Tensing. Circulation 2002;106:1684-1689 - Van Dijk N, Quertieri F, Blanc JJ, Garcia-Cevera R, Brignole M, Moya A, Wieling W. Effectiveness of physical counterpressure maneuvers in preventing vasovagal syncope: the Physical Counterpressure Manoeuvres Trial (PC Trial). J Am Coll Cardiol 2006;17:1652-1657. Treatment approaches that are now sometimes advised include:-	Thank you for your comment. We have removed parts of the recommendations that can be construed as relating to treatment, because, as stated, the guideline is not scoped to cover treatment and we have not reviewed the literature systematically.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
						: - leg crossing as a preventive measure during prolonged standing - whole body tensing with manoeuvres like buttock clenching if mild symptoms occur - squatting if a faint is imminent However, we acknowledge that one of the common features of "convulsive Reflex Syncope" is sudden onset of T-LOC without warning, where these manoeuvres would not be useful.	
SH	STARS - Syncope Trust And Reflex anoxic Seizures	44	Full	24	19	life style advices: Comment: consider to add water drinking	Thank you for your comment. We have removed parts of the recommendations that can be construed as relating to treatment, because, as stated, the guideline is not scoped to cover treatment and we have not reviewed the literature systematically.
SH	STARS - Syncope Trust	45	Full	27	General	Schematics Comment: clever, but very hard to follow schematic by overload of information.	This will be professionally typeset in the final Quick Reference Guide.

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	And Reflex anoxic Seizures						
SH	STARS - Syncope Trust And Reflex anoxic Seizures	46	Full	27	General	box D: *Comment*: 6 P's lack "absence of post-event amnesia or disorientation"	The recommendation for vasovagal syncope is a differential diagnosis for VVS compared with all other forms of TLoC. It is therefore in two sequential parts – exclusion of predictors in favour of all other types of TLoC, and then specific indicators for vasovagal syncope (usually in comparison with other forms of syncope). Post-event amnesia and disorientation are predictors for epileptic seizures and have been included in that recommendation. The recommendation for vasovagal syncope states that 'there are no features that predict an alternative diagnosis', so a lack of post-event amnesia or disorientation is covered.
SH	STARS - Syncope Trust And Reflex	47	Full	29	5	Definition of T-LOC *Comment:* The definition is different from the ESC guidelines definition, which is by far the most authoritative multidisciplinary "global" definition.	Thank you for your comment. We have modified the text to try to provide a clearer definition. This does not conflict with the wording in the ESC guidelines on syncope.

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	anoxic Seizures						
SH	STARS - Syncope Trust And Reflex anoxic Seizures	48	Full	35	1.5	This paragraph does not make sufficient reference to the limitations of the findings reported here. This analysis is primarily based on in-patient data. The changes in in-patient data seem to reflect a change in the presentation of T-LOC, no increase in the condition. It is very well documented that the number of patients admitted with T-LOC only represents a small minority of patients presenting with T-LOC to doctors (mainly in primary care but also in A&E). See general comments point 3	Limitations of the HES data mentioned on page 31. Only inpatient data is available. Data for outpatients not validated as yet.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	49	Full	36	1	Little difference was noted in the mean age of patients. Comment: in the general population there is a bimodal age distribution with a huge peak in teenagers and young adults, but this group does not present often to a medical setting.	We are interpreting the data available. It reflects the limitations of data availability
SH	STARS	5	Full	45	1.3	Comment. There has not been in increase in the condition	Accepted

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	- Syncope Trust And Reflex anoxic Seizures	0				in Wales but an increase of the number of patients presenting to secondary care!	
SH	STARS - Syncope Trust And Reflex anoxic Seizures	51	Full	55	4	"described by patients as blackout" *Comment:* "blackout" is a term for T-LOC which is in common parlance in the UK, and is defined as "transient loss of consciousness" in the Oxford English Dictionary. However, it must be acknowledged that this is not a strictly scientific term, but one which can be used with confidence when talking to patients, relatives, non-specialist doctors and doctors indifferent specialties. It is not in wide use in other countries, even English-speaking ones. At the same time the STARS MAC endorses the use of the correct term "T-LOC", which is interchangeable with blackout in the UK, but not elsewhere. Once again, publishing the NICE Guidance with a comprehensive and detailed Glossary of Terms would help spread understanding, pointing out the scientifically correct term, and common substitutes. (see line 23).	The Guideline has been prepared for use in the NHS in England and Wales, and uses terminology that is appropriate for these countries.

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SH	STARS - Syncope Trust And Reflex anoxic Seizures	52	Full	55	7	"which are probably the most common. Comment: cardiovascular disorders and in particular reflex syncope are by far the most common cause of TLOC in the population, which you seem to refer to since you say it occurs in 50% of the population. "Just as an example the frequency of epileptic seizures in the population in the young is about 1%, of reflex syncope about 30%.	We agree
SH	STARS - Syncope Trust And Reflex anoxic Seizures	53	Full	56	13 &18	Comment: Orthostatic hypertension should read Hypotension.	Thank you, this has been changed
SH	STARS - Syncope Trust	54	Full	57	General	Blackout clinics. Comment. See above.	See response above

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
	And Reflex anoxic Seizures						
SH	STARS - Syncope Trust And Reflex anoxic Seizures	55	Full	83	General	Prevalence is estimated to be approximately 25%. Comment: At an earlier point you mention almost 50% has experienced T-LOC.	Prevalence rates vary with different study groups – this figure comes from USA Air Force personnel lifetime experience. Following your comment we will include the Framingham study that reports a 42% prevalence which captures a broader group to age 70yrs
SH	STARS - Syncope Trust And Reflex anoxic Seizures	56	Full	88	General	**Glossary and Abbreviations:** *Comments.* The definitions on page 13 are not always the same **Black out** is now defined almost identical to syncope. Blackout should be defined as "transient loss of consciousness", and is interchangeable with T-LOC in the UK. **Carotid sinus syncope.** Tachyarrhythmias are not part of the reflex induced by pressure on the carotid sinus. A	Thank you for your comments. The definition of the term "Blackout" that was included here was clearly not that of syncope. We have emphasised in the text that people commonly use "blackout" to refer to an episode of TLoC. We have modified the definition of blackout for greater clarity.

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						distinction should be made between spontaneous and inducible carotid sinus syndrome (see Moya et al. ESC Guideline) **Faint.** Please be more specific. Faint should be defined as "T-LOC/blackout caused by reflex syncope" **Presyncope vs Prodrome.** Are these identical terms? **Situational syncope.** See comment on page 13 **Transient Loss of Consciousness.** Preferred term for blackout. Total agreement here. Please use T-LOC instead of blackout throughout the document.	This was a transcription error that had been spotted but not corrected before the guideline went out for consultation. We have modified the definitions to provide greater clarity regarding carotid sinus syncope and the clinical syndrome in which that occurs spontaneously. The term faint in its common usage refers specifically to vasovagal syncope which is only one type of neurally mediated or reflex\syncope. We have therefore left this definition unchanged. These are not identical terms and have therefore been defined accordingly. Definition has been modified appropriately. We have mostly used TLoC, but have to recognise that people use common parlance and that many people and their clinicians are comfortable with the use of "blackout" in this context. Another stakeholder has argued strongly in favour of "blackout".
SH	STARS - Syncope Trust And	57	Full	94	8,11 & 16	First mention of "psychogenic nonepileptic seizures" (PNES)– called "psychogenic seizures" in the first part of the document. The document should use one term. The most commonly used term in the UK is "nonepileptic attack disorder". Alternatively, the document could use the term "dissociative seizures" used in the ICD-10.	The GDG agreed on the term PNES and have added this to the glossary.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
	Reflex anoxic Seizures						
SH	STARS - Syncope Trust And Reflex anoxic Seizures	58	Full	97	General	**Pre-T-LOC** - How long was the pre-TLOC warning. *Comment:* Before black out should read before loss of consciousness	The section referred to in the comment contains the results of the diagnostic simulation, which was used to inform GDG discussions. This is a record of what was said in this simulation and so cannot be edited or added to retrospectively. We have now moved this section to Appendix D5.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	59	Full	97	General	**The T-LOC event itself** - How long was the attack? 30 minutes is unlikely to be syncope. *Comment. Definition of a*ttack is unclear (not mentioned in the glossary). This section refers to the T-LOC event itself. 'How long did loss of consciousness last?'seems more appropriate. We do not understand the 30 minutes criterium. > 5 minutes loss of unconsciousness is very unusual for syncope. Was the blackout related to posture or environment *Comment*: should read 'was the T-LOC related'.	The section referred to in the comment contains the results of the diagnostic simulation, which was used to inform GDG discussions. This is a record of what was said in this simulation and so cannot be edited or added to retrospectively. We have now moved this section to Appendix D5.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
SH	STARS - Syncope Trust And Reflex anoxic Seizures	60	Full	97	General	**3. Eye witness account** *Comment:* Information about myoclonic jerks, eyes open vs closed etc could be included	The section referred to in the comment contains the results of the diagnostic simulation, which was used to inform GDG discussions. This is a record of what was said in this simulation and so cannot be edited or added to retrospectively. We have now moved this section to Appendix D5.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	61	Full	97	General	**4. Post T-LOC** **-** Were there prolonged symptoms. Epilepsy more likely to have post symptoms. *Common:* prolonged symptoms are not defined. Syncope can have very prolonged symptoms of weakness and tendency to faint. **Missing: postprandial hypotension. An important underdiagnosed condition in the elderly**	The section referred to in the comment contains the results of the diagnostic simulation, which was used to inform GDG discussions. This is a record of what was said in this simulation and so cannot be edited or added to retrospectively. We have now moved this section to Appendix D5.
SH	STARS - Syncope Trust	62	Full	100	General	*Comments.* See general comments. Vascular syncope is a new terminology not defined in the glossary. P.100, l. 29: PNES again	Thank you for your comment. We have deleted the term vascular syncope and used neurally mediated syncope and orthostatic hypotension instead.

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	And Reflex anoxic Seizures						
SH	STARS - Syncope Trust And Reflex anoxic Seizures	63	Full	101	General	Orthostatic hypotension *Comment:* medication is by far the most common cause of orthostatic hypotension.	Thank you for your comment. This has been noted in the recommendation about medication history.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	64	Full	108	1.21	"Pseudoseizures" and "Psychogenic nonepileptic attacks" – two further terms for the same thing. Again, the Glossary of Terms should mention the correct scientific term, (or nominate it!!), and acceptable alternatives	The GDG agreed on the term PNES and have added this to the glossary. However, when reporting a study, we generally use the terminology in the study to avoid mis-understanding.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
SH	STARS - Syncope Trust And Reflex anoxic Seizures	65	Full	109	1.26	PNES	We have reported the terms as used in the particular study
SH	STARS - Syncope Trust And Reflex anoxic Seizures	66	Full	110	1.1	PNES	We have reported the terms as used in the particular study
SH	STARS - Syncope	67	Full	110	1.26	PNES	We have reported the terms as used in the particular study, in this case corrected to 'psychogenic pseudosyncope'

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
	Trust And Reflex anoxic Seizures						
SH	STARS - Syncope Trust And Reflex anoxic Seizures	68	Full	114	1.1	PNES	We have reported the terms as used in the particular study, in this case corrected to 'psychogenic pseudosyncope'
SH	STARS - Syncope Trust And Reflex anoxic Seizur	69	Full	117	1.18	PNES	We have reported the terms as used in the particular study, in this case corrected to 'psychogenic pseudosyncope'

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
	es						
SH	STARS - Syncope Trust And Reflex anoxic Seizures	70	Full	124	1.24	NPES (sic.)	We have reported the terms as used in the particular study, in this case corrected to 'psychogenic pseudosyncope'
SH	STARS - Syncope Trust And Reflex anoxic Seizures	71	Full	129	General	Do the authors mean "bedwetting" or "urinary incontinence"?	Regarding 'bedwetting' - we have reported the signs and symptoms exactly as described in the study. A second study (now included) investigated 'urinary incontinence' as a predictor for epileptic seizures compared with syncope and found no significant difference. This heterogeneity between studies could be caused by differences in study quality or could be differences in terminology - we assume the term 'bedwetting' is more specific (meaning urinary incontinence at night). In view of this uncertainty, we did not include either term as a predictor for epilepsy.
SH	STARS - Synco	72	Full	145	1.3	"Psychogenic pseudosyncope" (also on same page – referring to the same study: PNES)	We have reported the terms as used in the particular study, in this case corrected to 'psychogenic pseudosyncope'

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
	pe Trust And Reflex anoxic Seizures						
SH	STARS - Syncope Trust And Reflex anoxic Seizures	73	Full	156	1.15	"bedwetting" again	See earlier response
SH	STARS - Syncope Trust And Reflex anoxic	74	Full	161	1.17	PNES	We have reported the terms as used in the particular study, in this case corrected to 'psychogenic pseudosyncope'. Much of this section has been revised.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
	Seizures						
SH	STARS - Syncope Trust And Reflex anoxic Seizures	75	Full	162	General	Misquotes the ESC Guidelines on OH by omitting the fall in diastolic BP of 10mm Hg. Brignole 2006 seems at one stage to have been dismissed because it only focused on 'good' arrhythmias. May we assure you that the study reported all the arrhythmias that were found.	We have reported the definition used by the van Dijk 2008 authors as this is the index test being investigated. We agree the authors have misquoted the ESC guidelines. Page 232 says that it was possible to extract only the 'good arrhythmias'. This means that, although the Brignole 2006 study reported all the arrhythmias, we we able to isolate the acceptable arrhythmias for this study, so that the study was considered unbiased. The study was not dismissed at all. We have re-written this sentence in the full version to make it clearer.
SH	STARS - Syncope Trust And Reflex anoxic Seizures	76	Full	174	1.26	PNES	Noted. Please refer to other responses with regard to PNES.
SH	STARS -	77	Full	176	1.5	PNES	We have reported the terms as used in the particular study, in this case correctly reported as PNES.

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	Syncope Trust And Reflex anoxic Seizures						
SH	STARS - Syncope Trust And Reflex anoxic Seizures	78	Full	176	1.29	on p.6 the authors mention a cut-off of 450ms for a prolonged QTc, here they mention 460ms for women and 440ms for men. They may want to be consistent in this document.	As explained in other responses, in the body of the full guideline we report the findings of studies. This is a report of these studies and quotes their figures and uses their terminology. This is reported here. The view of the GDG was that one cut off for both men and women of 450ms is more practical and unlikely to miss anyone at high risk.
SH	STARS - Syncope Trust And Reflex	79	Full	204	1.15	For the first time in this document the category "unexplained TLOC" includes epilepsy and PNES. It would be better if categories / terms were used consistently throughout the document, and refer to the Glossary.	This section is reporting the clinical questions as they were developed at the start of the guideline to inform the searches. It would be inaccurate to change retrospectively the language now. In addition, when reporting trials, we use the language used in the study to avoid confusion.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
	anoxic Seizures						We have however, revised the terminology in the recommendations to make this more consistent. .
SH	STARS - Syncope Trust And Reflex anoxic Seizures	80	Full	335	General	Tachycardia Comment; There is no discussion of syncope in the context of VT/SVTs that we have found but we may have missed it.	Tachycardia during TLoC was included as an outcome in both the diagnostic reviews and the economic modelling. The post diagnostic outcomes of VT during syncope, including treatment with an ICD, have been explicitly included within the model.
SH	The Joint Royal Colleges Ambulance Service Liaison Committee	1	Full	General	General	Overall the Joint Royal Colleges Ambulance Liaison Committee welcomes the proposed guidance on transient loss of consciousness in adults.	Noted with thanks

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SH	The Joint Royal Colleges Ambulance Service Liaison Committee	2	Full	General	General	The JRCALC would welcome guidance on patients who can safely be left at home.	Noted with thanks. We have added to the recommendations and explicitly stated which patients should be taken to the ED and who can be left at home and what to do further with these people.